Studies Towards the Synthesis of Nakadomarin A

A thesis presented to University College London in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Jai Krishan Chavda

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***I,** Jai Krishan Chavda, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.*

ABSTRACT

Nakadomarin A is a manzamine related alkaloid isolated from the marine sponge *Amphimedon* off the coast of the Kerama islands, Okinawa. This alkaloid has been found to possess numerous biological activities including anti-tumour, anti-fungal and anti-bacterial. This along with its intricate structure, consisting of a fused tetracyclic ring system flanked by two macrocycles, has prompted numerous investigations into its synthesis. This thesis describes various attempts at the construction of the tetracyclic ring system. Key steps in the synthetic plan include a thio-Claisen rearrangement to establish two of the four stereocentres in the molecule, and an iminium ion/furan cyclisation to form the carbocyclic B ring.

The initial investigations focused on the development of a method for formation of the carbocyclic B ring. This was achieved by treatment of a secondary γ-thiolactam with an α-bromoester; the resulting iminium ion effected electrophilic substitution on a pendant furan to form the desired 5-membered ring. Unfortunately this approach was unsuccessful with more complex substrates, and the use of an acyl chloride as a more reactive electrophile in place of the ester led to only small amounts of the expected product. Development of the thio-Claisen reaction required the synthesis of a furan with a *Z*-3-bromoprop-1-enyl substituent in the 3-position. Unfortunately, all attempts to prepare this furan were unsuccessful, with significant isomerisation to the *E*-isomer observed.

A revised strategy was to develop a tandem thio-Claisen/*C*-acylation protocol to establish the required stereogenic centres for nakadomarin. Initial attempts at acylating a tertiary thiolactam had proved unsuccessful, thus an alternative strategy was considered that involved conversion of the thioamide to an *N*,*S*-ketene acetal following *S*-allylation. The resultant ketene acetal could behave as a nucleophile and undergo reaction with an acylating agent. This hypothesis was tested through allylation with *E* cinnamyl bromide followed by acylation with numerous acylating agents. Unfortunately, the *N,S*-ketene acetal underwent thio-Claisen rearrangement before acylation could take place. However, allylation with *Z* cinnamyl bromide allowed for an acylation of the resultant ketene acetal with phenyl isocyanate, giving an intermediate which then underwent spontaneous thio-Claisen rearrangement to give the desired thiolactam adduct with excellent diastereoselectivity.

For My Mum

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ABBREVIATIONS

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Ala	Alanine
An	Anisole
aq.	Aqueous
Ar	Aryl
Arg	Arginine
Asn	Asparagine
ATR	Attenuated Total Reflectance
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
brsm	Based on recovered starting material
Bs	Brosylate
Bu	Butyl
CAN	Ceric ammonium nitrate
CDK	Cyclin-dependant kinase
CI	Chemical ionisation
COSY	Correlation spectroscopy
m-CPBA	*meta*-Chloroperoxybenzoic acid
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
Cys	Cysteine
d	Day
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric excess
DEPT	Distortionless enhancement by polarisation transfer
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide

DMTSF	Dimethyl(methylthio)sulfonium tetrafluoroborate
DNA	Deoxyribonucleic acid
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EI	Electron ionisation
eq.	Equivalent
ES	Electrospray
Et	Ethyl
FTIR	Fourier transform infrared spectroscopy
Fur	Furan
Gly	Glycine
h	Hour
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HMQC	Heteronuclear multiple quantum coherance
HRMS	High resolution mass spectrometry
IBX	2-Iodoxybenzoic acid
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
Leu	Leucine
LHMDS	Lithium hexamethyldisilazide
LDBB	Lithium di-*tert*-butylbiphenyl
lit.	Literature
Lys	Lysine
m.p.	Melting point
m/z	Mass to charge ratio
MAJ	Major diastereoisomer
MDAP	Mass directed auto purification system
Me	Methyl
Mes	Mesityl
Met	Methionine
min	Minute
MIN	Minor diastereoisomer
Ms	Methanesulfonyl
MS	Mass spectrometry

NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
Ph	Phenyl
PMB	*para*-Methoxybenzyl
Pr	Propyl
Pyr	Pyridine
RCM	Ring closing metathesis
rt	Room temperature
Ser	Serine
TBAC	Tetra-*n*-butylammonium chloride
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBME	*tert*-Butylmethylether
TBS	*tert*-Butyldimethylsilyl
Tex	thexyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyran
Thr	Threonine
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	4-Toluenesulfonyl
Tyr	Tyrosine
UCL	University College London

CONTENTS

1. INTRODUCTION

1.1. Isolation of compounds from the marine environment

The marine ecosystem is a vast habitat and is home to a great number of organisms from which scientists are able to isolate natural products which may have some very interesting properties. Some of these natural products have had their biological activities tested and are now being used as medicines. For example *Conus magnus* is a cone snail that paralyses its prey using a poison tipped barb.[1] A compound extracted from the poison is a pain killer which is much stronger than morphine. Ziconotide (**1**) is branded as Prialt® and is the synthetic form of the cone snail peptide, conotoxin. It is a non-opioid treatment for chronic pain and is delivered intrathecally. Studies carried out in animals show that it is a N-type calcium channel blocker.[2]

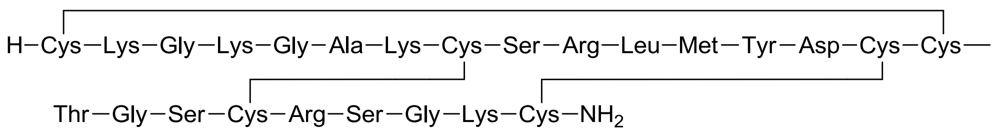

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Figure 1: Ziconotide.[1]

Another marine organism, *Ecteinascidia turbinate*, is a Caribbean and Mediterranean sea squirt which produces a compound that has anti-tumour activity for soft-tissue sarcomas. Trabectidin (**2**) has been branded Yondelis® by PharmMar and is currently awaiting marketing approval from the European Medicines agency.[1] The two examples above show that the marine environment is a viable source for the discovery of new medicines.

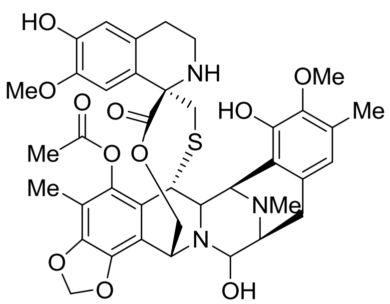

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Figure 2: Trabectidin.[3]

1.2. The Manzamines

The manzamines are an important class of polycyclic alkaloids and are isolated from marine sponges of genera *Amphimedon*, *Acanthostrongylophora*, *Haliclona*, *Xestospongia*, and *Ircinia*.[4] Manzamine A (**3**), the first of the manzamine alkaloids to be discovered, was isolated by Higa and co-workers as a hydrochloride salt from the Okinawan marine sponge *Haliclona* sp. in 1986.[5]

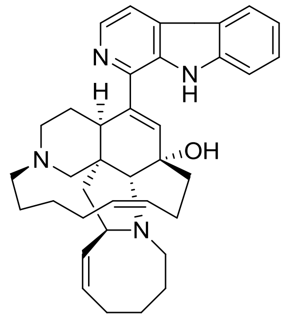

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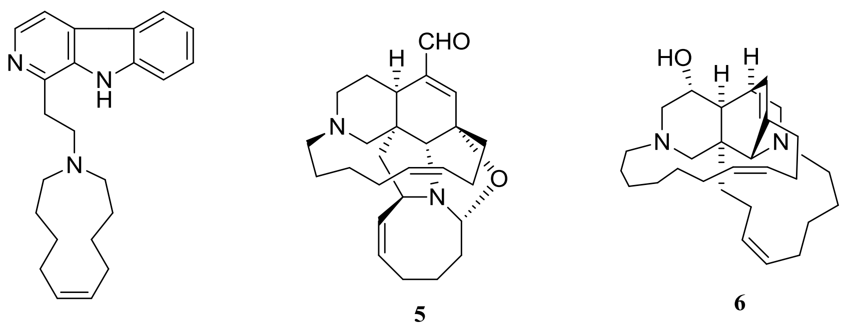
Figure 3: Manzamine A (**3**).

The manzamine alkaloids have been shown to possess various bioactivities, which include cytotoxicity, anti-microbial and anti-inflammatory properties. One biological property of the manzamine alkaloids is their effectiveness at combating malaria. They have been shown to be more potent and less toxic than the more established treatments which use compounds such as chloroquinine.[6] The structures of the manzamine alkaloids can vary widely and the examples shown in Figure 4 demonstrate this variation.



4 **5** **6**

Figure 4: Examples of manzamine alkaloids; manzamine C (**4**), oxaircinal A (**5**), xestocyclamine A (**6**).

1.3. Nakadomarin

Nakadomarin A (**7**, Figure 5) was isolated by Kobayashi and co-workers from the sponge *Amphimedon* sp. (SS-264) which was collected off the coast of the Kerama Islands, Okinawa.[7]

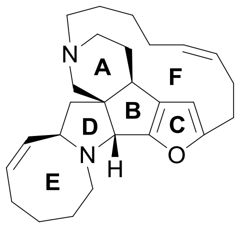


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Figure 5: Nakadomarin A (**7**).

Kobayashi isolated alkaloid **7** during investigations into biogenetically related precursors to the manzamine alkaloids. The structure of nakadomarin was elucidated through spectroscopic analysis, and revealed an intricate structure consisting of a fused tetracyclic ABCD core incorporating pyrrolidine, piperidine and furan heterocycles, fused to two larger rings – the 8-membered E ring and the 15-membered F ring. Nakadomarin A is the first manzamine related alkaloid to be discovered that has a furan ring in its structure.

1.3.1. Biological activity

Nakadomarin A displays a broad range of biological activities, including cytotoxicity against murine lymphoma L1210 cells (IC_{50} 1.3 μg/mL) and inhibitory activity against cyclin dependent kinase 4 (IC_{50} 9.9 μg/mL). Inhibition of the CDK4 enzyme arrests the cell replication cycle at the G1 growth phase before the cell enters its DNA replication stage. Nakadomarin A also exhibits anti-microbial activity against a fungus (*Trichophyton mentagrophytes*, MIC 23 μg/mL) and a Gram-positive bacterium (*Corynebacterium xerosis* MIC 11 μg/mL).[7, 8]

1.3.2. Biosynthetic pathway

Work on a plausible biosynthetic pathway to nakadomarin A and some of the other manzamine alkaloids has been carried out by the groups of Baldwin and Kobayashi.[7, 9] During their work on the biosynthesis of the manzamines, Baldwin and Whitehead postulated that the complex manzamine A alkaloid was formed from 4 relatively simple compounds. The biosynthesis of nakadomarin A according to Kobayashi and the work on the pathway to manzamine A carried out by Baldwin share a common intermediate; ircinal A (**8**), which is a natural product in its own right (Figure 6). Combining the work of these two groups we can see how nakadomarin A may be formed, thus showing how most of the manzamine alkaloids, although structurally quite distinct, could arise from the same simple compounds.

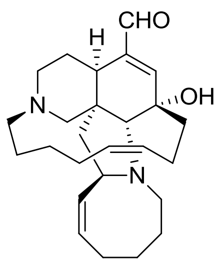

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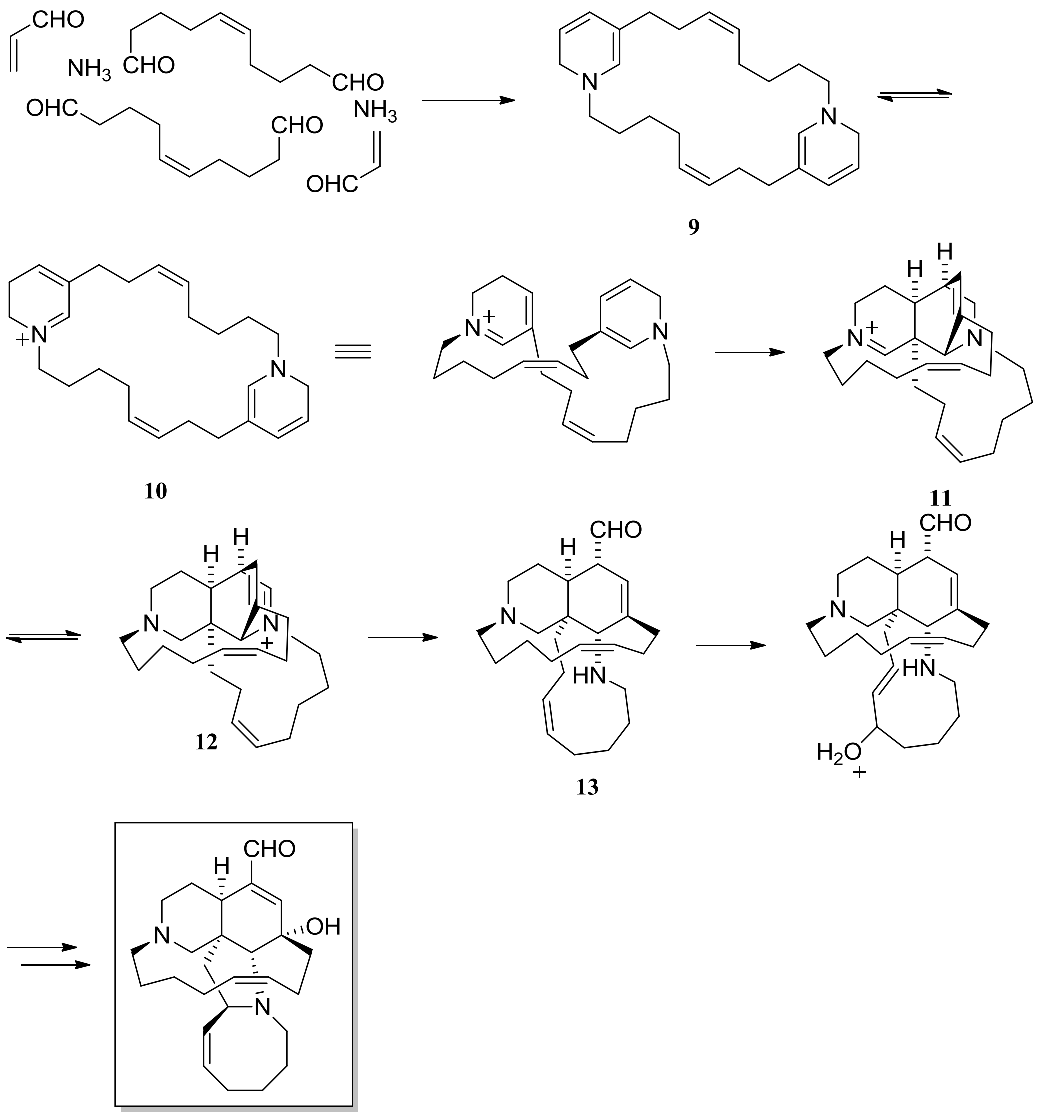
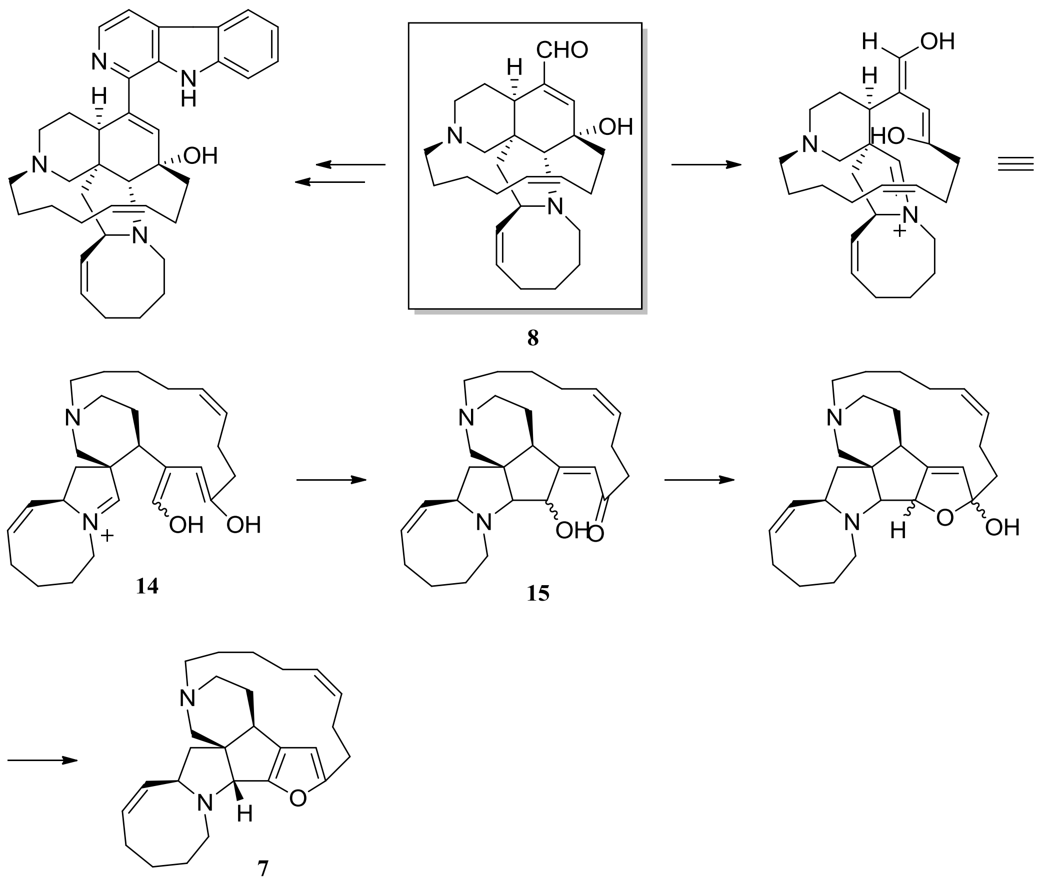
Figure 6: Ircinal A

Baldwin's pathway to manzamine A begins with a reductive coupling of two C_3 units and two C_{10} units with two molecules of ammonia, giving macrocycle **9**. Protonation of **9** to give dihydropyridinium cation **10** is followed by a Diels-Alder reaction to give adduct **11**, which can also undergo a potential side reaction, a reduction of the iminium ion to give keramaphidin B, another manzamine alkaloid. Redox exchange between the piperidine rings of **11** gives **12** which is hydrolysed to aldehyde **13**. Oxidations of **13** followed by ring-closure gives common intermediate ircinal A (**8**).



Scheme 1: Biogenetic pathway to ircinal A as proposed by Baldwin and Kobayashi.

Scheme 2 shows the completion of the biosynthetic pathway to nakadomarin A and manzamine A. Condensation of ircinal A with tryptophan gives manzamine A. The pathway from ircinal A to nakadomarin A begins with a retro-vinylogous Mannich reaction of alkaloid **11,** giving intermediate iminium ion **14** which undergoes a vinylogous Mannich reaction to form the carbocycle in **15**. Cyclisation followed by a loss of water to aromatise to the furan ring gives nakadomarin A. Although not proposed by Kobayashi, another possible biosynthetic route could be envisaged which would involve **14** undergoing cyclisation to form the furan prior to C-C bond formation.



Scheme 2: Completion of the biosynthesis of nakadomarin A.

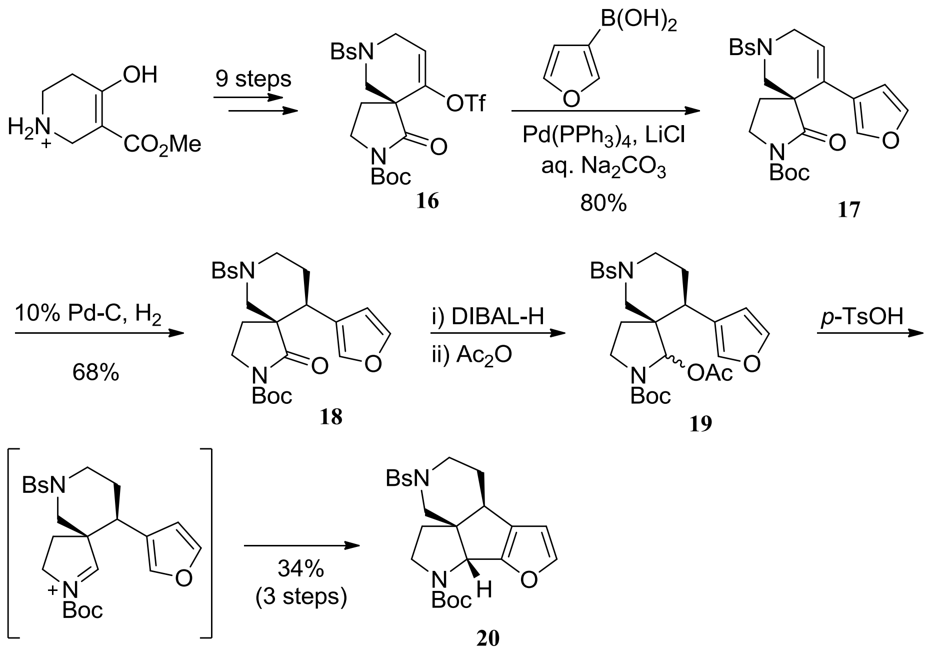
1.3.3. Previous work – total syntheses

The structure of nakadomarin A offers a substantial challenge to the synthetic organic chemist; at the heart of the compound is a fused tetracyclic ring system consisting of different heterocycles which is flanked by 2 macrocycles. It also has the distinguishing feature of being the only manzamine alkaloid to have a furan ring in its structure. This coupled with its interesting biological properties and low availability from natural sources (1.8×10^{-3} % of sponge wet weight) has piqued the interest of many research groups. There have been nine total syntheses to date with multiple offerings from the Nishida group, who published the first total synthesis of the unnatural enantiomer,[10] and the Dixon group. Formal syntheses have also been published as well as approaches to the core and work concentrating on specific aspects of the structure, for example Fürstner's development of an alkyne metathesis to form the 15-membered macrocycle.[11] The following sections outline the previous syntheses and synthetic work carried out on nakadomarin A by other research groups.

1.3.3.1. Nishida's syntheses

The Nishida group was one of the first to publish a synthesis of the core of nakadomarin A in 2001.[12] A key step in Nishida's approach was the cyclisation of a furan onto an iminium ion to form the carbocyclic B ring.

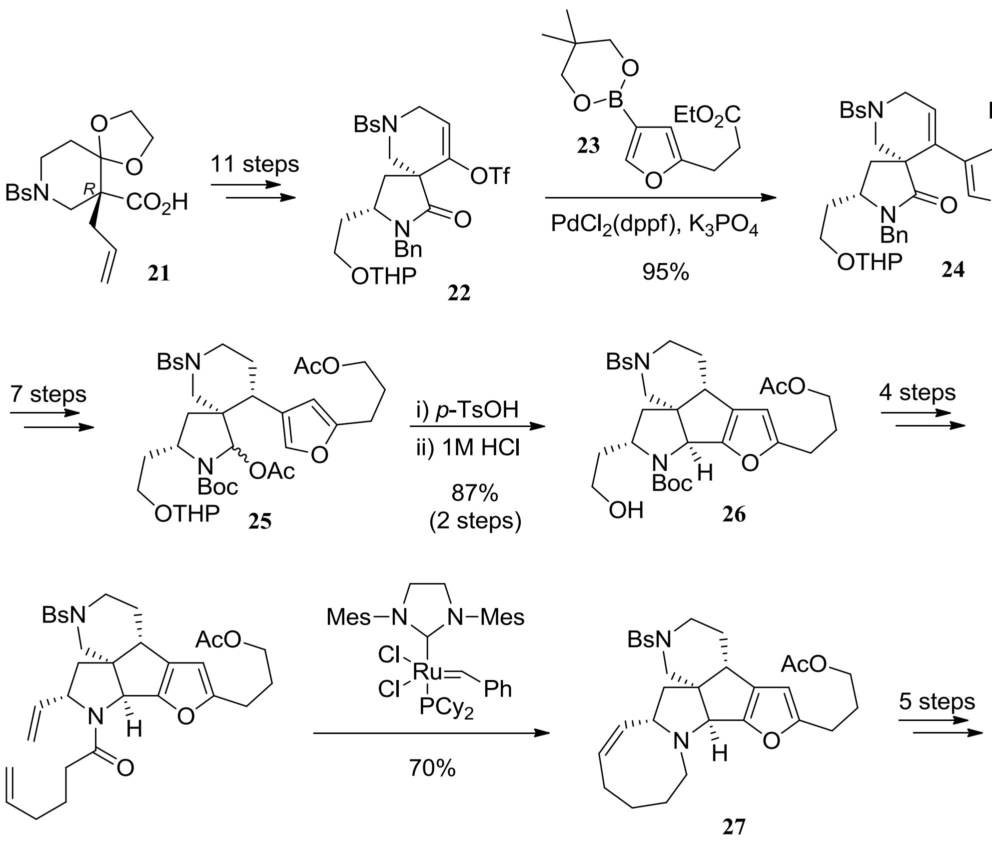
The synthesis began from methyl 4-oxo-3-piperidinecarboxylate hydrochloride which was converted to enol triflate **16** in 9 steps. Introduction of the furan ring to the substrate was carried out by Suzuki-Miyaura coupling of the enol triflate with furan-3-boronic acid. Hydrogenation of **17** using 10% Pd-C proceeded cleanly with no observed reduction of the furan ring. The γ-lactam **18** was reduced using DIBAL-H followed by conversion of the hydroxy group to an acetate to give hemiaminal **19**. *p*-TsOH was used to effect generation of an iminium ion which underwent spontaneous cyclisation to give tetracyclic core **20** (Scheme 3).

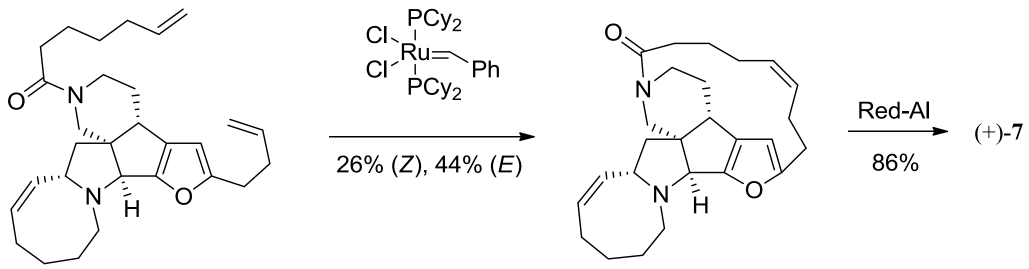


Scheme 3: Nishida's synthesis of the ABCD ring system.

Nishida followed the successful development of the furan/acyliminium ion methodology by applying it in the synthesis of nakadomarin A. At the time the work was commenced, the absolute configuration of the natural product was unknown; the enantiomer targeted by Nishida was shown to be the non-natural enantiomer.

Scheme 4 highlights some of the key steps from Nishida's synthesis. The total synthesis began with (*R*)-**21**, which was obtained through resolution of readily available racemic **21** using (+)-cinchonine. This was converted, in 11 steps, to cross-coupling precursor **22** which crucially contained a THP protected alcohol side chain, essential for the formation of the 8-membered E ring. Suzuki-Miyaura coupling of enol triflate **22** with borate **23** gave **24**. This step also installed a side chain which would be used later on in the synthesis to construct the 15-membered F ring. Cross-coupling product **24** was converted to cyclisation precursor **25** in 7 steps. The cyclisation was carried out using the conditions developed in the synthesis of the core, thus successfully giving tetracycle **26**. Attention now turned to the synthesis of the two macrocycles; both rings were constructed using alkene ring closing metathesis. The formation of the E ring was effected using the second generation Grubbs catalyst and was relatively straightforward, giving **27** in a good yield. However the second RCM reaction proved to be more problematic, with the unwanted and thermodynamically more favourable *E* isomer being formed as the major product. The two isomers were separable, and the *Z* isomer was subjected to a reduction using Red-Al and thus gave (+)-nakadomarin A.



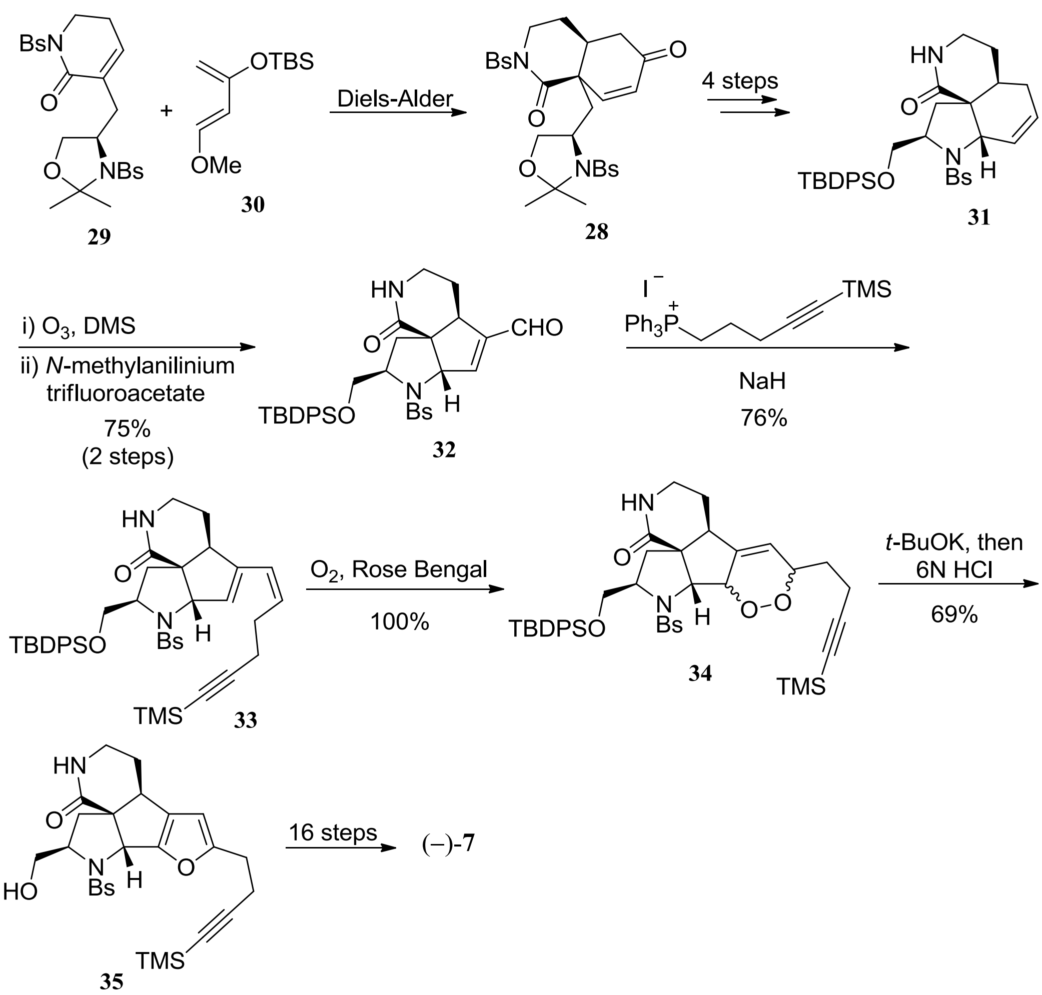


Scheme 4: Nishida's synthesis of (+)-nakadomarin A.

Nishida completed the synthesis of (+)-**7** in 37 linear steps. An abundance of protecting group manipulations resulted in a lengthy synthesis, however it did allow the determination of the absolute configuration of (−)-**7**, and all 4 chiral centres of the natural product were assigned as *R*.

With the completion of the total synthesis of (+)-nakadomarin A, Nishida embarked on a second synthesis, this time targeting the naturally occurring enantiomer.[13] In Nishida's previous synthesis an enantiomerically pure intermediate was obtained by a resolution of a carboxylic acid as a cinchonium salt. However, the preparation of the opposite natural enantiomer was inefficient, which resulted in the development of a new synthetic route to the natural enantiomer of nakadomarin A.

Nishida began his synthesis of (−)-**7** with the formation of functionalised tetrahydroisoquinoline **28**, which was obtained *via* Diels-Alder reaction between **29** and siloxydiene **30** (Scheme 5). Chiral dienophile **29** was prepared in 10 steps from L-serine.



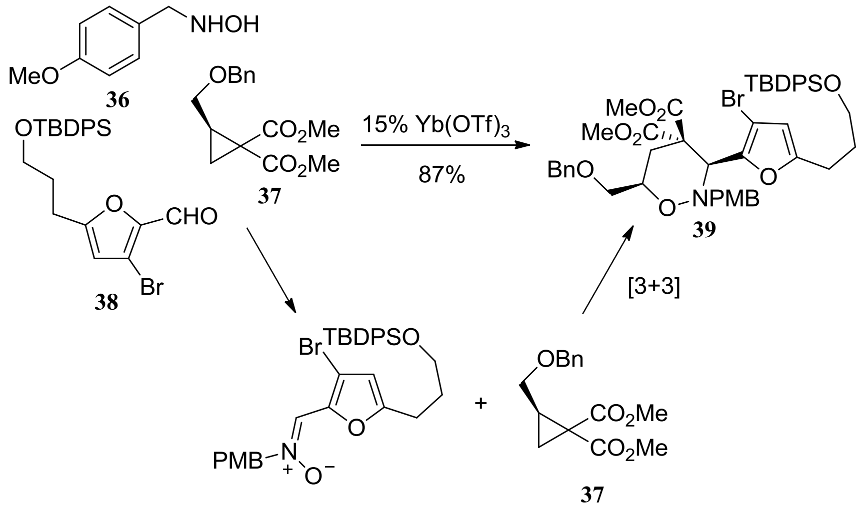
Scheme 5: Key steps from Nishida's synthesis of (–)-**7**.

Key steps in the route included a ring contraction; the cleavage of the 6-membered ring of **31** by ozonolysis using O_3 gave an unstable dialdehyde, which was recyclised to a 5-membered ring by aldol condensation with *N*-methylanilinium trifluoroacetate to form compound **32**. Another key step was the formation of the furan ring *via* the conversion of (*Z*)-diene **33** to peroxide **34** using singlet oxygen, which gave the product as a mixture of diastereoisomers. Peroxide **34** was treated with *t*-BuOK to form the furan ring. This was followed by the addition of strong acid to remove the TBDPS group which gave tetracycle **35**. A further 16 steps were required to complete the synthesis of (–)-**7**.

Nishida completed the first synthesis of the natural enantiomer of nakadomarin A in 36 linear steps, a small improvement on the previous synthesis.

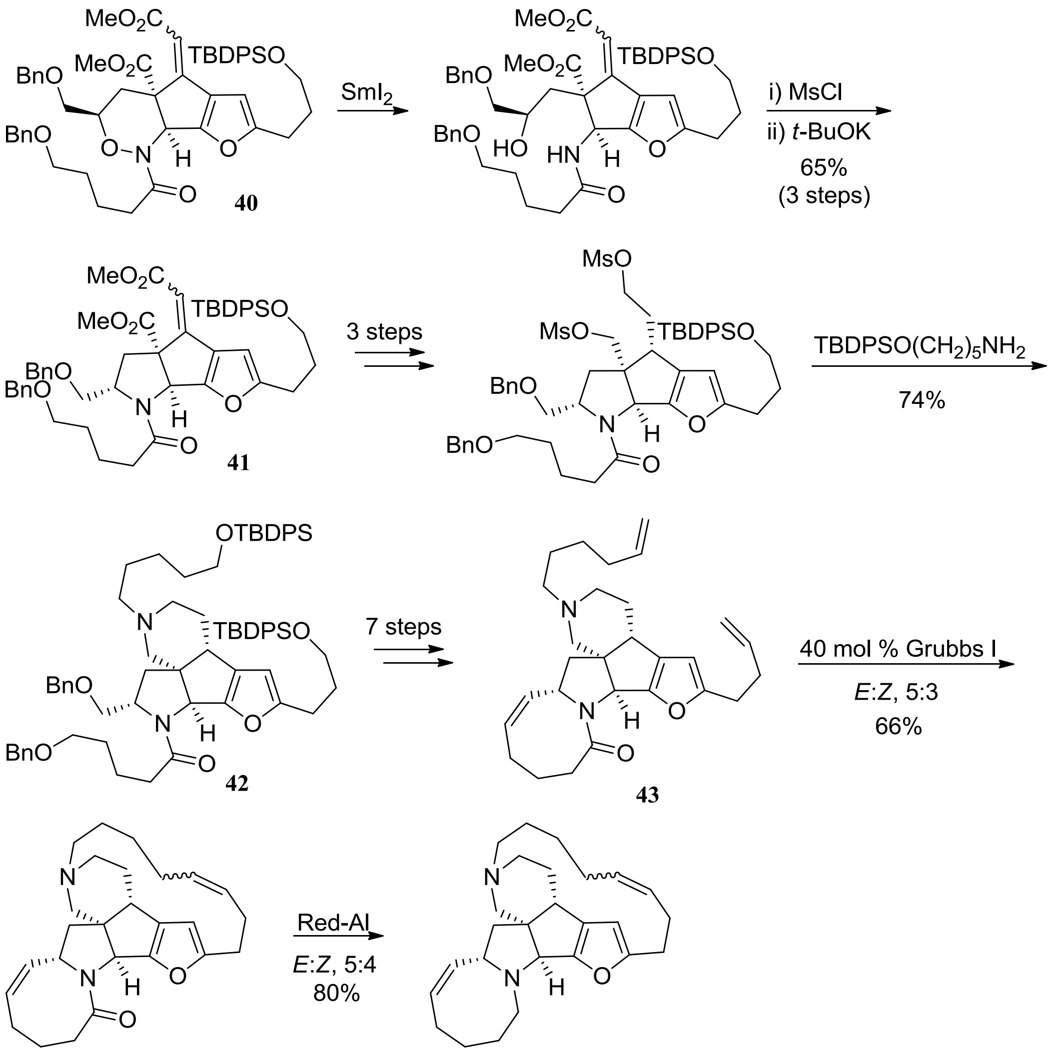
1.3.3.2. Kerr's synthesis

The next synthesis of nakadomarin A was published by Kerr and co-workers, who targeted the unnatural isomer.[14] The highlight of the synthesis was a three component cycloaddition reaction of hydroxylamine **36**, cyclopropane **37** and aldehyde **38** to give functionalised tetrahydro-1,2-oxazine **39** using $Yb(OTf)_3$ as a Lewis acid, which was developed previously by Kerr and used in the synthesis of the ABCD ring system (Scheme 6). The reaction proceeds *via* an *in situ* formation of a nitrone from hydroxylamine **36** and aldehyde **38**. The nitrone then undergoes stepwise dipolar cycloaddition with cyclopropane **37** to give oxazine **39**.



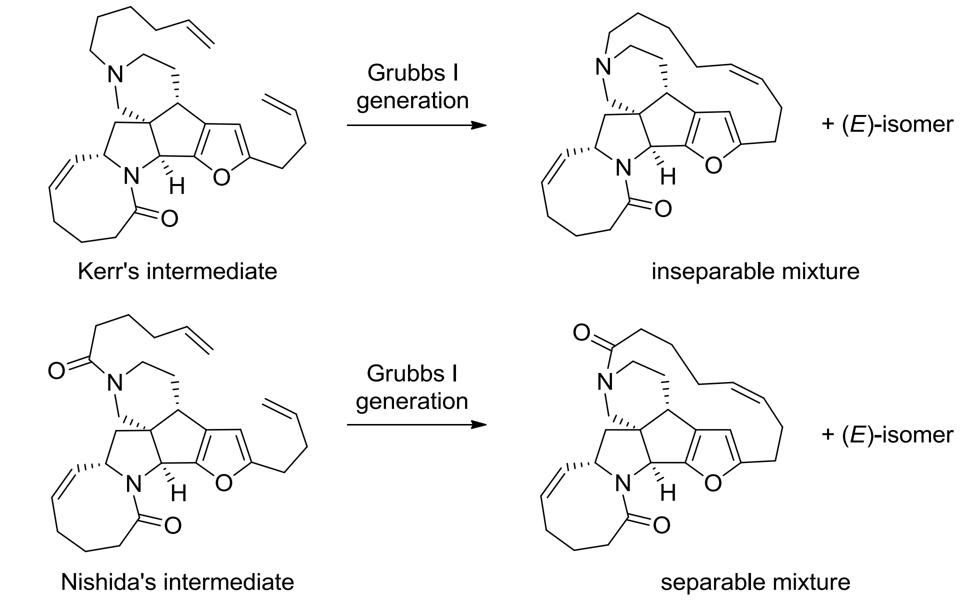
Scheme 6: Three component cycloaddition of hydroxylamine **36**, cyclopropane **37** and aldehyde **38** to give functionalised tetrahydro-1,2-oxazine **39**.

Another noteworthy transformation in the synthesis was a SmI_2 mediated cleavage of the N-O bond in **40**, which was followed by mesylation of the free hydroxyl group and cyclisation to install the pyrrolidine ring in **41**. The piperidine ring was synthesised by a double S_N2 alkylation using a protected aminoalcohol to give tetracyclic core **42**, which was then converted to diene **43** in 7 steps. Olefin metathesis was carried out on **43**, which gave the cyclised product as an inseparable mixture of isomers. The amide functionality of both isomers was reduced with Red-Al which gave (+)-**7** along with the unwanted *E*-isomer. Efforts at separating the product mixture using normal-phase chromatography were unsuccessful (Scheme 7).



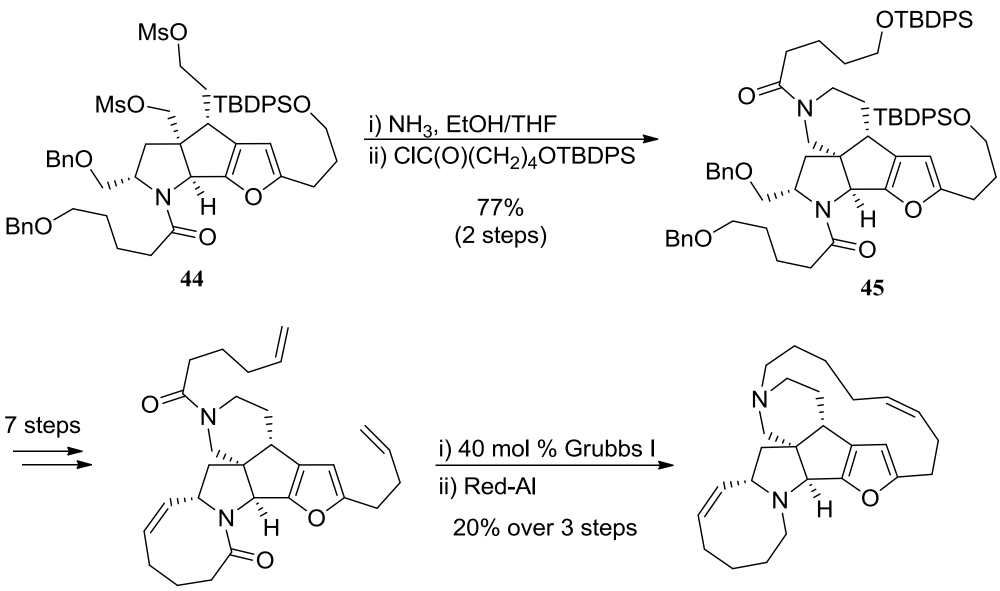
Scheme 7: Attempted synthesis of (+)-**7**. Inseparable mixture of isomers following lactam reduction led to a revision of the strategy.

While both Kerr and Nishida used an RCM reaction to close the F ring, in Kerr's case this led to an inseparable mixture of (+)-nakadomarin A (**7**) and its (*E*)-isomer. Nishida's substrate incorporated an additional amide functionality and in this case, it was possible to separate the geometric isomers from the RCM (Scheme 8).



Scheme 8: RCM reactions to form the 15-membered ring.

Kerr's route to the natural product was thus modified by treating dimesylate **44** with ethanolic ammonia to give a secondary amine, followed by acylation to give compound **45**. This allowed for the separation of the isomers obtained from the RCM reaction, thus allowing the successful synthesis of (+)-**7** in 29 linear steps, a marked improvement over the previous two syntheses (Scheme 9).

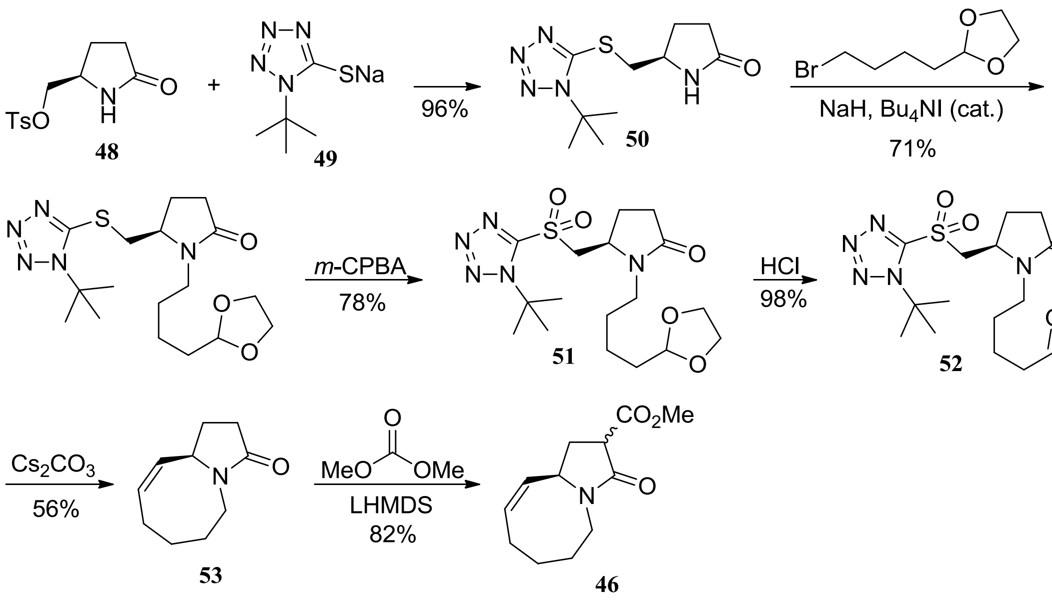


Scheme 9: Completion of the synthesis of nakadomarin A.

1.3.3.3. Dixon's syntheses

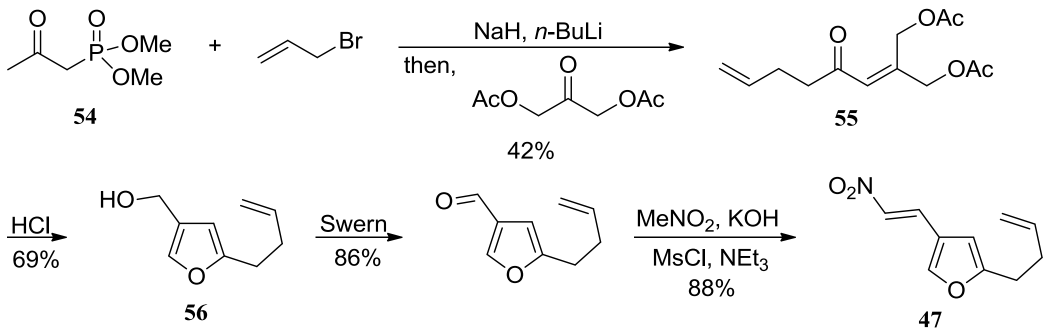
The Dixon group adopted a highly convergent strategy in their first synthesis of the naturally occurring enantiomer of **7**.[15] The route began with the syntheses of 8,5-bicyclic Michael donor **46** and nitro olefin **47**, both of which were synthesised from commercially available materials.

The synthesis of Michael donor **46** began with nucleophilic substitution of tosylate **48** with sodium thiolate **49** to give sulfide **50**. *N*-alkylation with 2-(4-bromobutyl)-1,3-dioxolane followed by oxidation of the sulfide gave sulfone **51**. Removal of the acetal protecting group afforded olefination precursor **52**. A Julia-Kocienski reaction was carried out using Cs_2CO_3 in wet THF/DMF which gave 8,5-bicyclic lactam **53**. Acylation with dimethyl carbonate gave Michael donor **46** (Scheme 10).



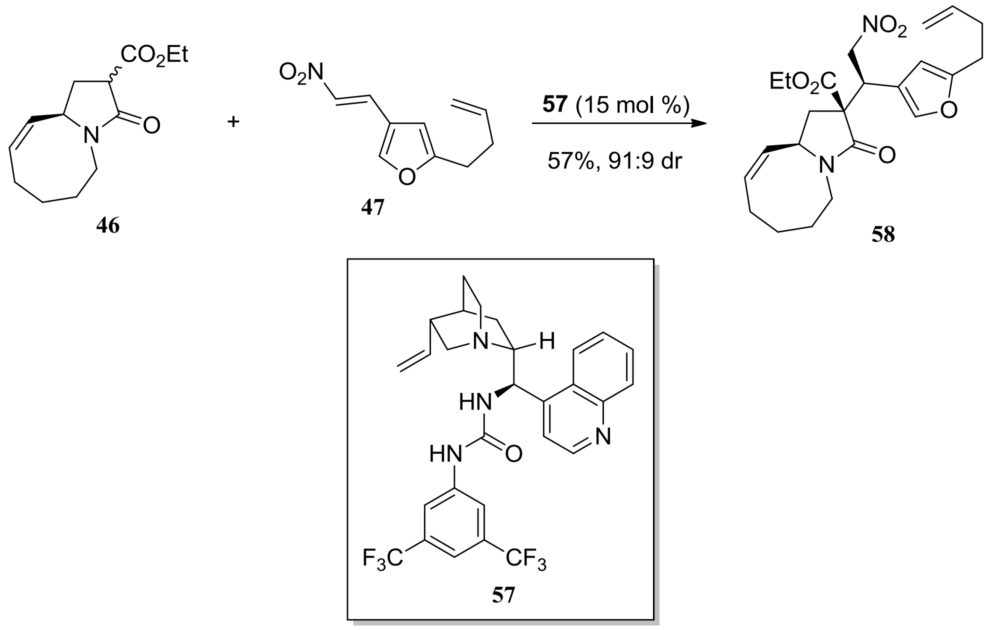
Scheme 10: Synthesis of Michael donor **46**.

The route to Michael acceptor **47** began with a one pot allylation/Horner-Wadsworth-Emmons reaction of phosphonate **54** with allyl bromide and 2-oxopropane-1,3-diyl diacetate to give enone **55**. This was converted to furanyl alcohol **56** *via* acid hydrolysis. Swern oxidation followed by condensation of the resultant aldehyde with $MeNO_2$ afforded nitro olefin **47** (Scheme 11).



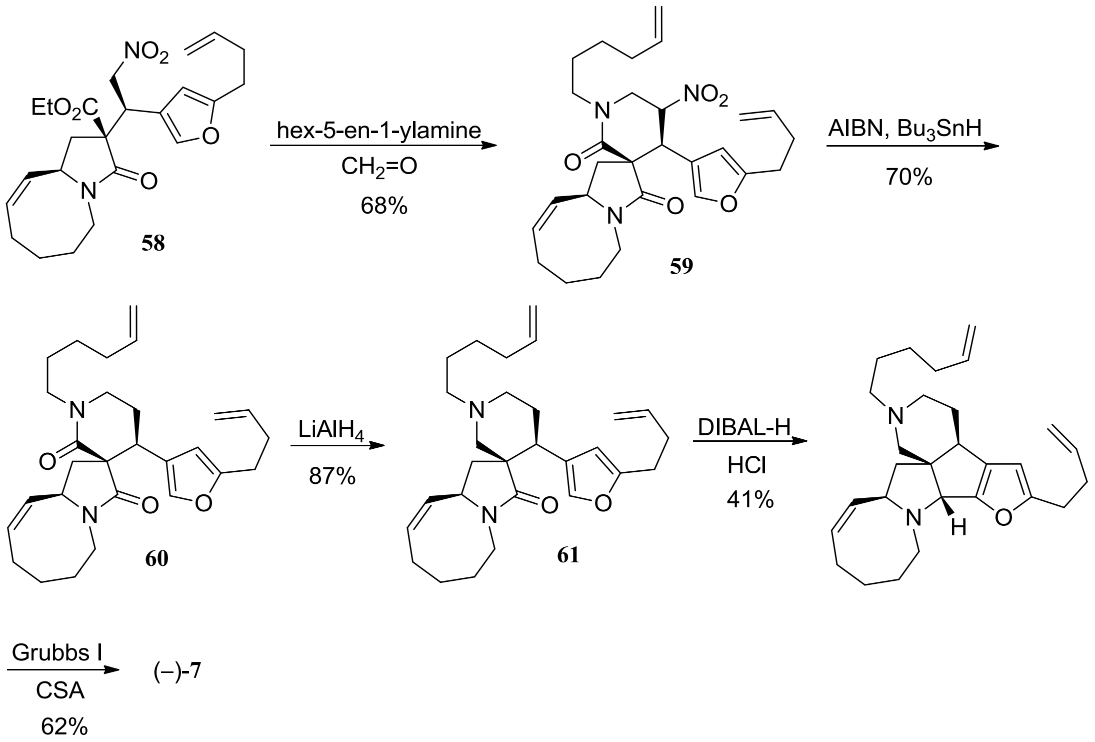
Scheme 11: Synthesis of Michael acceptor **47**.

The two components were subjected to a Michael addition, with good stereocontrol achieved through the use of bifunctional *Cinchona* catalyst **57**, giving adduct **58** in a good yield as a 10:1 mixture of diastereoisomers (Scheme 12).



Scheme 12: Synthesis of Michael adduct **58** using bifunctional *Cinchona* catalyst **57**.

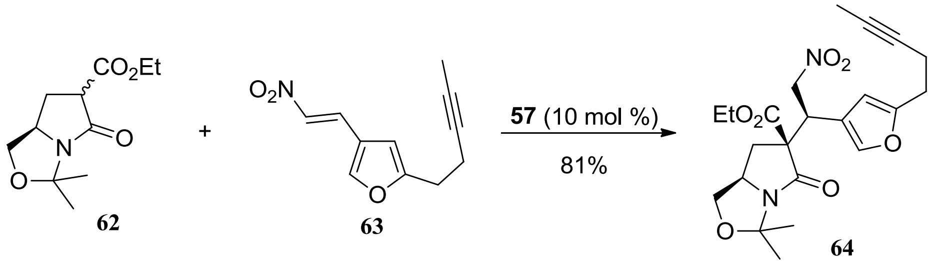
Focus next turned to the formation of the piperidine ring. Using previously developed conditions, the piperidine was synthesised through a three-component nitro-Mannich/lactamisation reaction which furnished the tetracyclic ACDE ring system **59** in a good yield.[16] A subsequent reduction of the nitro group using Bu_3SnH gave **60**. This was followed by a low temperature reduction using $LiAlH_4$, which only targeted the amide functionality of the A ring, and left the pyrrolidine-2-one group intact. A one pot partial reduction of the amide group of **61** and furan/iminium ion cyclisation gave the pentacyclic ring structure of (–)-**7**, with only the formation of the macrocyclic F ring left to complete the synthesis. Use of Grubbs' first-generation catalyst gave a mixture of isomers favouring the *E*-isomer, which was expected. However when the reaction was repeated in the presence of CSA, which protonated the amine functionalities in the compound, a more favourable ratio was achieved (63:37, *Z*:*E*) (Scheme 13).



Scheme 13: Completion of Dixon's first synthesis of (–)-nakadomarin A.

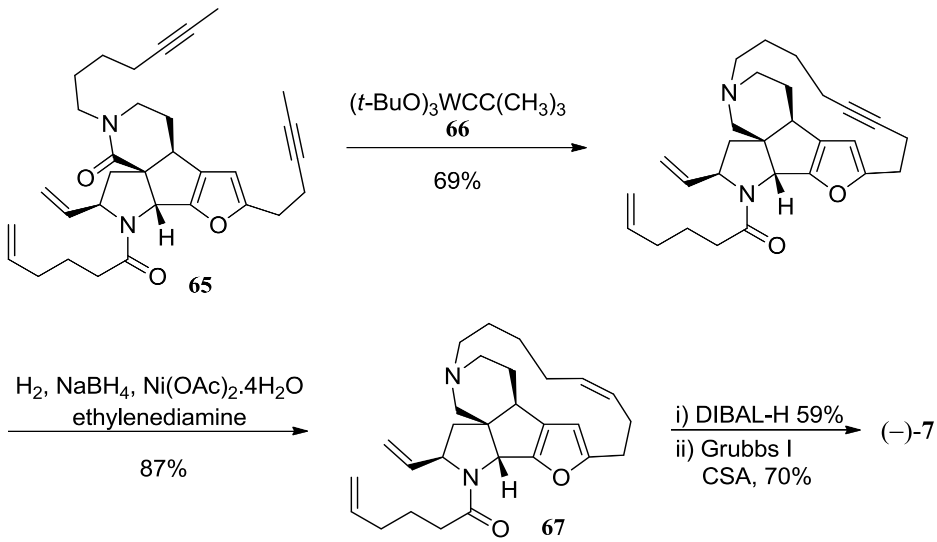
Dixon's synthesis of (–)-**7** was remarkably short; it was completed in almost half as many steps as the next shortest synthesis (16 in total, 12 linear). It was also remarkably efficient, providing 101 mg of (–)-**7**. However the Dixon group felt they could improve a few aspects of the synthesis, particularly the final RCM reaction.

In their next synthesis, the Dixon group adopted the alkyne RCM/*Z*-selective reduction methodology developed by Fürstner and co-workers.[17] The second synthesis also provided an opportunity to improve the Michael addition step, and so the new route began with a synthesis of isopropylidene derivative **62**, which was completed in 2 steps from D-pyroglutaminol.[18] Additionally, an alternative nitro olefin was synthesised (compound **63**) containing the alkyne moiety needed for the alkyne RCM. Opting to change to Michael donor **62** had the desired effect; the ratio improved to 18:1 (up from 10:1) giving adduct **64** as the correct diastereoisomer in a very good yield as a single product (Scheme 14).



Scheme 14: Improved Michael addition using isopropylidene derivative **64** and bifunctional *Cinchona* catalyst **57**.

The adduct **64** was converted to diyne **65** using a route similar to that described previously, and alkyne RCM of diyne **65** was completed through the use of the Schrock tungsten neopentylidene catalyst **66**, followed by a *Z*-selective reduction to **67** using *in situ* generated nickel boride in the presence of ethylenediamine to form the F ring. The synthesis was completed with a reduction of the amide functionality with DIBAL-H and an alkene RCM to form the 8-membered E ring, thus synthesising (–)-**7** in 19 linear steps (Scheme 15).

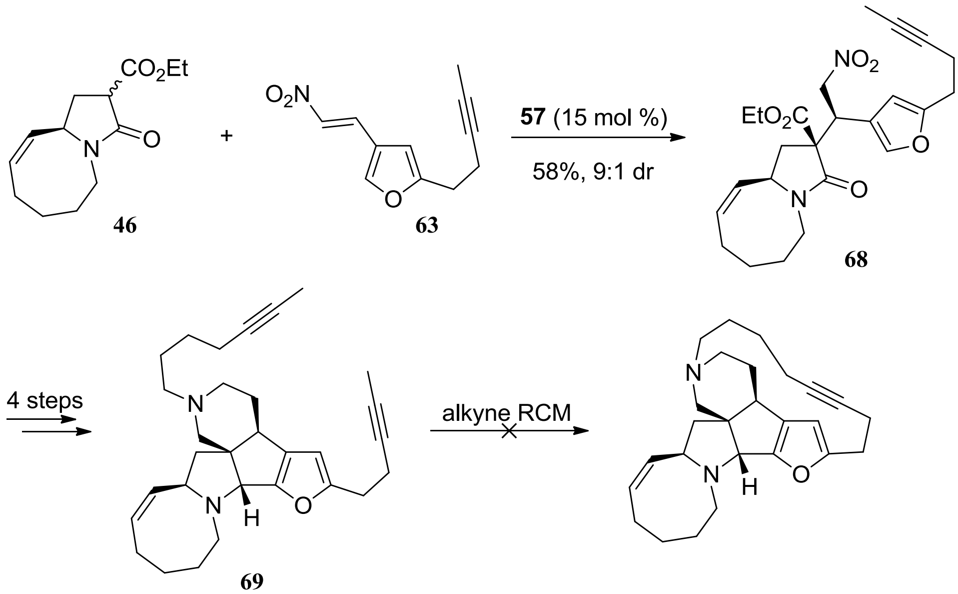


Scheme 15: Alkyne metathesis followed by a Z-selective reduction.

The problems with *E*/*Z* selectivity had been addressed, however the higher step count prompted the Dixon group to carry out a third synthesis, which combined the alkyne

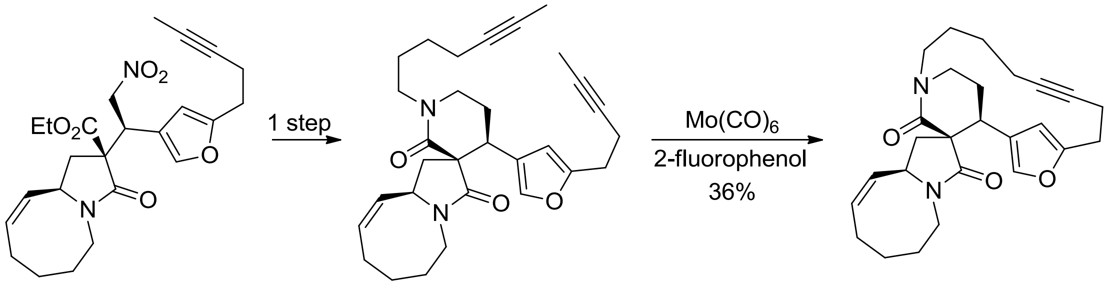
RCM/Z-selective hydrogenation with the more convergent strategy used in the first synthesis in the pursuit of a more efficient route.[19]

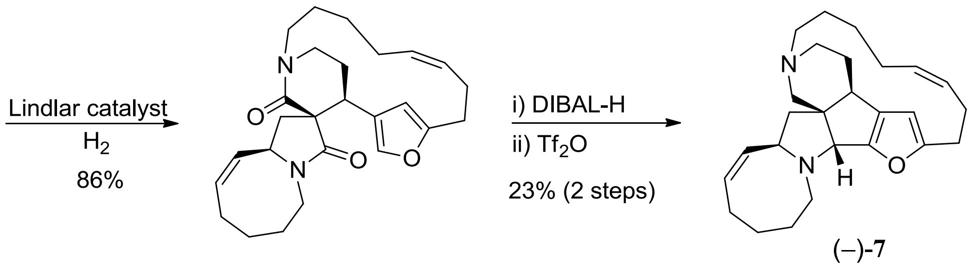
The synthesis began with the construction of bicycle **46** and nitro olefin **63**, following identical procedures used in the previous two syntheses. Michael addition gave **68**, which was then converted to diyne **69** in 4 steps. Attempts at completing the alkyne RCM were unsuccessful, thus the route was modified (Scheme 16).



Scheme 16: Attempted alkyne RCM of diyne **69**.

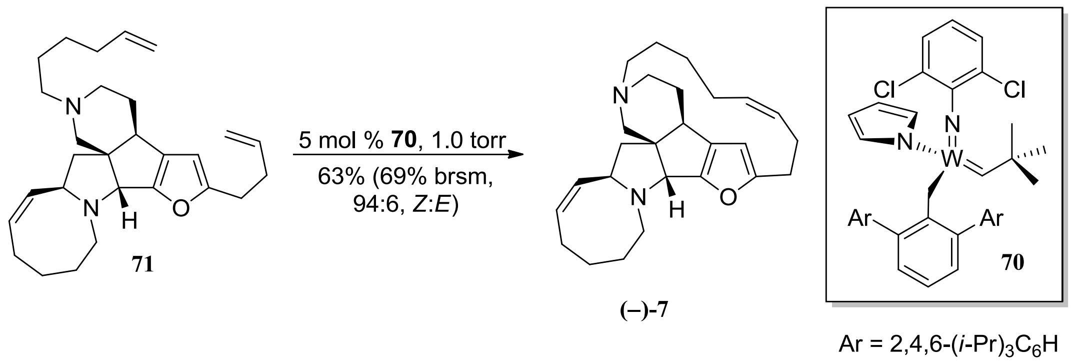
The alkyne RCM/*syn*-reduction was carried out earlier in the synthesis, and was followed by a reduction of the lactam group and the furan/iminium ion cyclisation to successfully give (–)-**7**. The step count was slightly higher than the first synthesis; it was completed in 13 steps. However the problems with isomeric mixtures in the RCM reaction had been successfully addressed (Scheme 17).





Scheme 17: Completion of Dixon's third synthesis of (–)-**7**.

The final evolution of the Dixon synthesis saw a return to an alkene RCM in the construction of the macrocyclic F ring (Scheme 18).[20] The alkene RCM was realised by using tungsten alkylidene catalyst **70** in a reduced pressure environment, which provided the F ring in an extremely selective manner (94:6, *Z*:*E* ratio) and a good yield (63%, 69% based on recovered **71**).

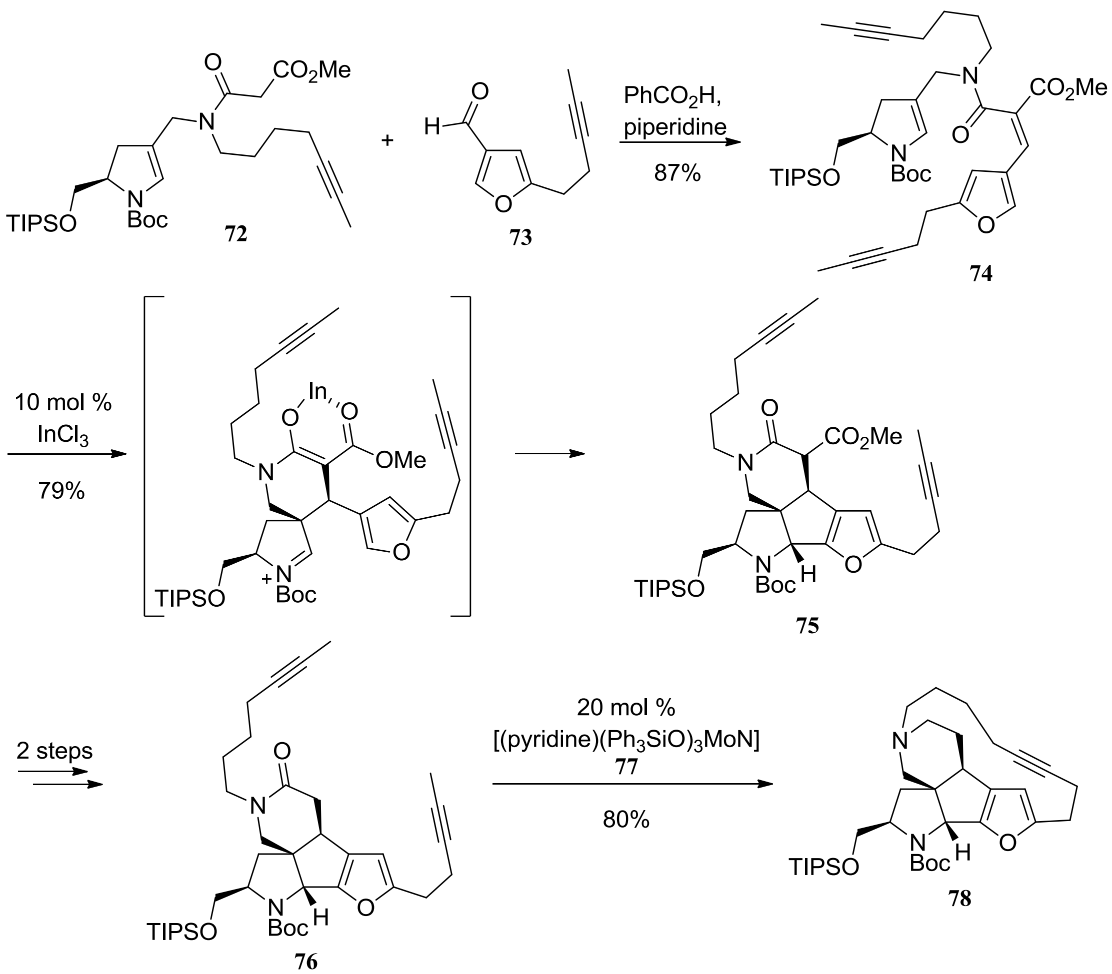


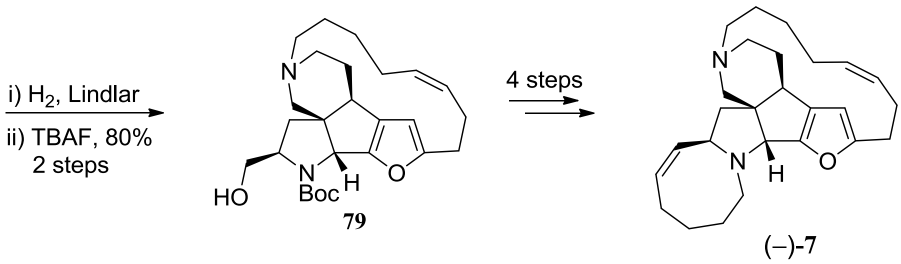
Scheme 18: Final alkene RCM step in the synthesis of (–)-**7**.

1.3.3.4. Funk's synthesis

Funk and co-workers followed the publication of Dixon's first route with a synthesis of (–)-nakadomarin A, which built upon work they previously carried out in the synthesis of the tetracyclic core.[21] Funk opted for a convergent synthesis, which also had the added distinction of being the first route to nakadomarin A to include an alkyne RCM/*syn*-reduction to synthesise the F ring.

The synthesis began with the formation of Boc-protected dihydropyrrole **72** and furaldehyde **73**, which were synthesised from commercially available materials in 8 and 4 steps respectively. Knoevenagel condensation of the two components gave amide **74** as the *E*-isomer. The next transformation involved a one-pot enecarbamate Michael addition/*N*-acyliminium ion cyclisation using $InCl_3$. The reaction proceeded *via* a Lewis acid promoted Michael addition, which formed the 6-membered A ring and generated an electron deficient iminium ion. This underwent nucleophilic attack from the furan ring to give carbocyclic C ring, thus forming the piperidine A ring and the carbocyclic ring B ring in a single step. Tetracycle **75** was converted to diyne **76** and was subjected to various alkyne metathesis conditions. The best result was obtained using molybdenum nitride complex **77**, giving cycloalkyne **78** in a good yield. The *Z*-selective hydrogenation was carried out using Lindlar's catalyst, giving the macrocyclic F ring. The crude product mixture was subjected to the next step; a removal of the silyl protecting group using TBAF, yielding alcohol **79**. Attention was then turned to the synthesis of the 8-membered E ring, which was finished in 4 steps, allowing the completion of the synthesis in 21 linear steps (Scheme 19).

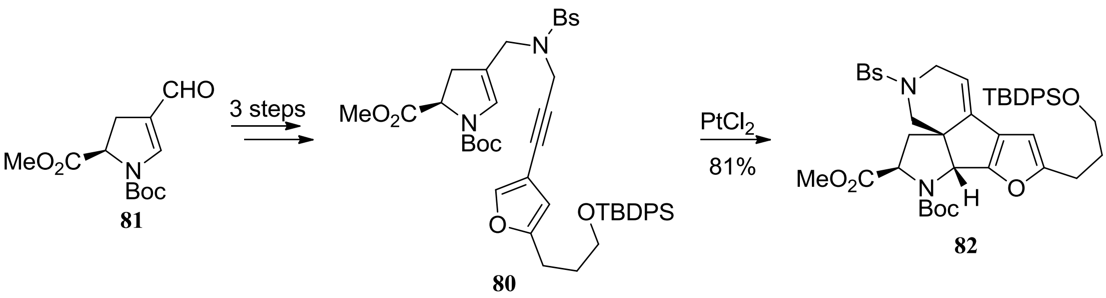


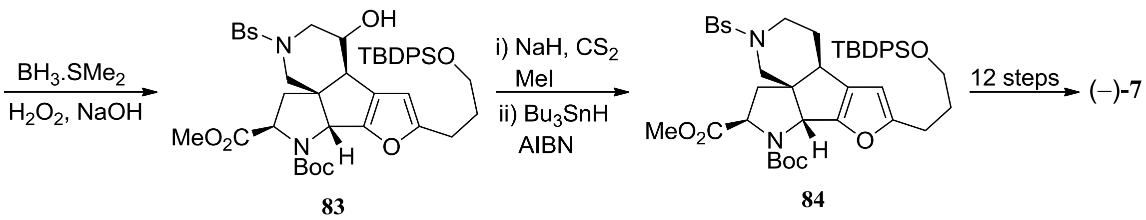


Scheme 19: Key steps from Funk's synthesis of (–)-**7** including a one-pot enecarbamate Michael addition/*N*-acyliminium ion cyclisation using $InCl_3$.

1.3.3.5. Zhai's synthesis

Zhai *et al*. adopted a similar approach to that of the Funk group, carrying out nucleophilic attack with a Boc-protected pyrrolidine and thereby generating an electron deficient iminium ion, which subsequently underwent nucleophilic attack from the furan ring. Previous work in the Zhai group had looked at the activation of an alkyne to nucleophilic attack using $PtCl_2$, which allowed for the completion of the ABCD ring system of the natural product, proving the viability of this approach.[22] This protocol was successfully applied to the total synthesis of the naturally occurring enantiomer of nakadomarin A.[23] Cyclisation precursor **80** was synthesised in 3 steps from aldehyde **81**. The cyclisation cascade was successfully carried out using $PtCl_2$, forming the A and B rings to give tetracycle **82** in a good yield. Reduction of the alkene in the A ring was accomplished through a hydroboration/oxidation to give **83**, which was subsequently converted to a xanthate followed by a Barton-McCombie deoxygenation to give the ABCD ring system. The synthesis was completed in 12 steps from **84**, with the Zhai group adopting a similar strategy to Dixon's first route in the synthesis of the F ring.



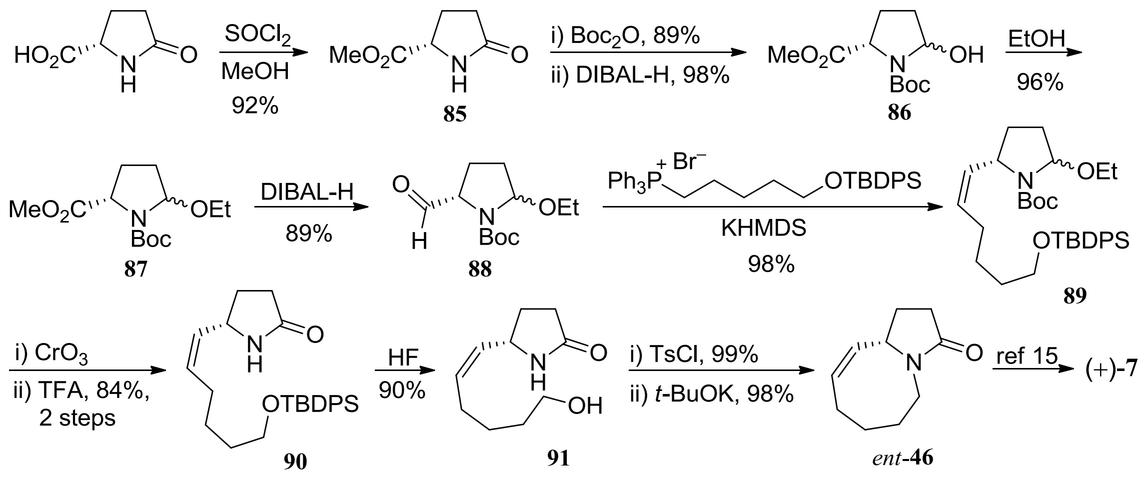


Scheme 20: Key steps from Zhai's synthesis of (–)-**7** including a $PtCl_2$ mediated cascade reaction.

1.3.4. Previous work – formal syntheses

1.3.4.1. Stockman's synthesis

In 2010, Stockman *et al*. published an improved synthesis of the enantiomer of a key building block in Dixon's synthesis of nakadomarin; the 8,5-bicyclic lactam.[24] The synthesis began from the commercially available L-pyroglutamic acid, which was converted to methyl ester **85** *via* an acyl chloride. Boc-protection followed by a partial reduction of the amide functionality gave hemiaminal **86**, which was converted to *N*,*O*-acetal **87**. Reduction of the methyl ester to aldehyde **88** was carried out using DIBAL-H. Wittig reaction furnished **89**, which was converted to **90** through oxidation to a lactam and removal of the Boc-protecting group. The final steps of the synthesis involved the formation of the 8-membered E ring, and were carried out by first removing the silyl protecting group to give free alcohol **91**. This was tosylated and cyclised using *t*-BuOK giving the desired 8,5-bicyclic lactam and thus completing the formal synthesis of (+)-**7** (Scheme 21).

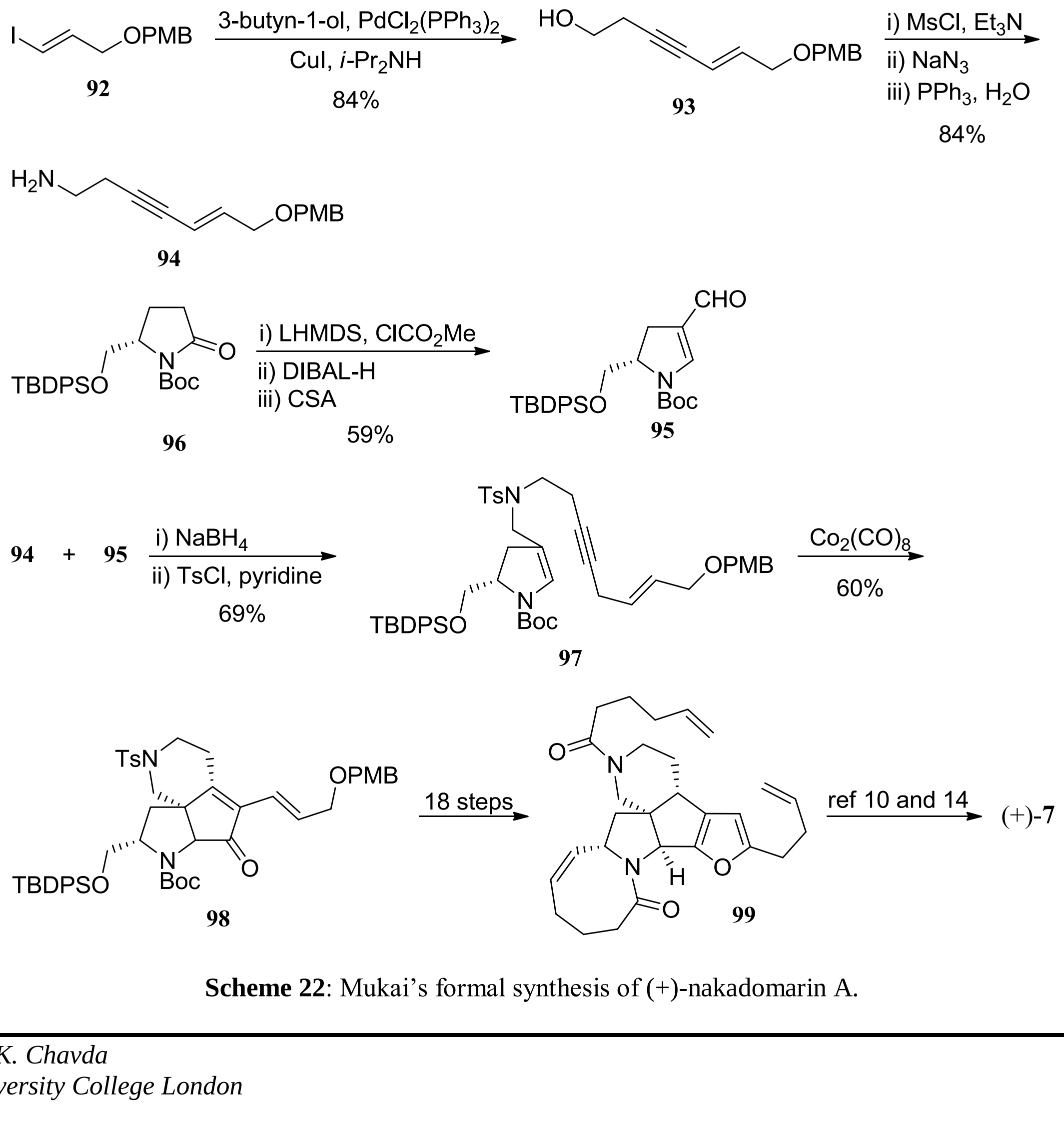


Scheme 21: Stockman's formal synthesis of (+)-**7**.

Although the route to *ent*-**46** was slightly longer (10 steps), the overall efficiency had been greatly improved with an increase in the overall yield from 29.2% to 49.2%.

1.3.4.2. Mukai's synthesis

The second formal synthesis of (+)-nakadomarin A was completed by Mukai *et al*.[25] The highlight of the synthesis was a Pauson-Khand reaction to synthesise the tricyclic ABD ring system. The synthesis began with Sonogashira reaction of vinyl iodide **92**, which gave enyne **93** which was then converted to amine **94**. This was achieved by conversion of the alcohol to an azide *via* a mesylate, followed by a Staudinger reaction to give amine **94**. The synthesis of **94** was followed with a preparation of aldehyde **95** from lactam **96**. Reductive amination of **94** with **95** followed by tosylation of the resultant secondary amine gave **97**. Precursor **97** was subjected to a Pauson-Khand reaction using dicobalt octacarbonyl, which gave tricycle **98**. This was converted to triene **99** in 18 steps to complete the formal synthesis (Scheme 22).



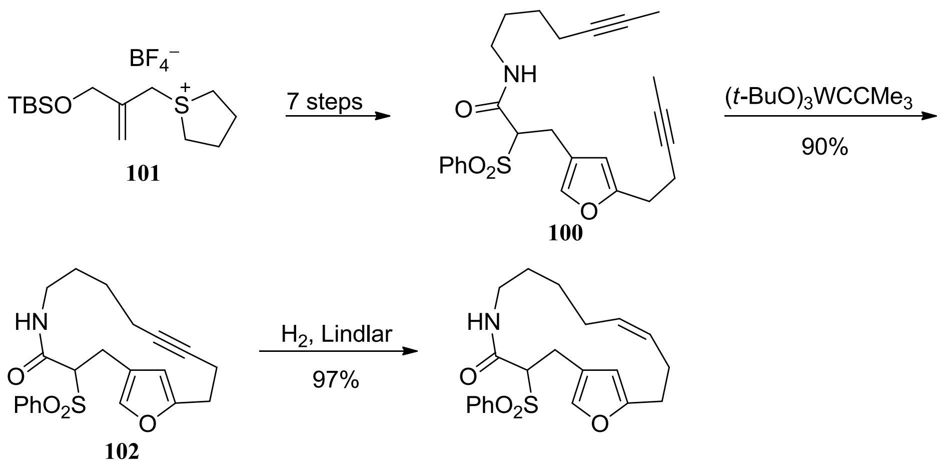
Scheme 22: Mukai's formal synthesis of (+)-nakadomarin A.

1.3.5. Previous work – synthetic approaches

1.3.5.1. Fürstner's approaches

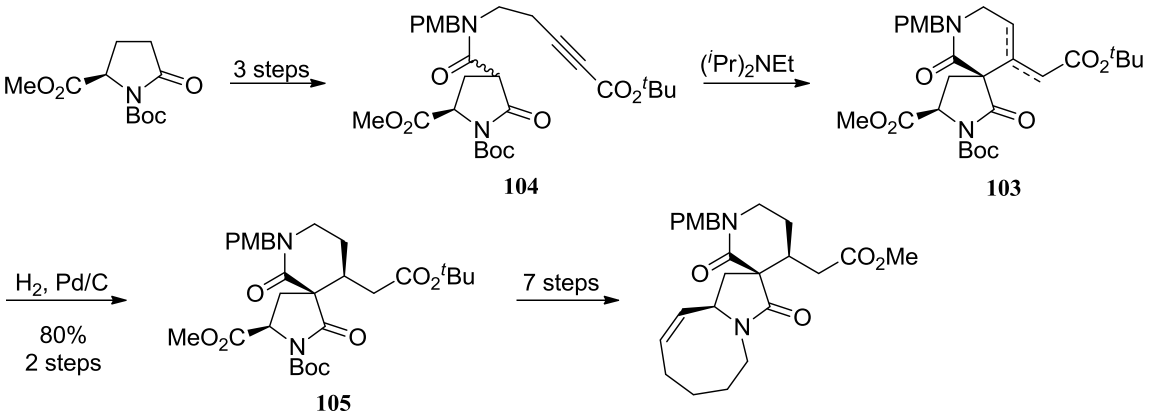
In 1999, the Fürstner group published a synthesis of the macrocyclic F ring of nakadomarin A.[17] The approach taken was to carry out an alkyne RCM of a diyne to give a cycloalkyne, followed by a *Z*-selective hydrogenation, which allowed the group to minimise the formation of the thermodynamically favoured *E*-alkene. This method has since been used by the Dixon and Funk groups in their syntheses of (–)-**7**.

The alkyne RCM precursor **100** was synthesised in 7 steps from sulfonium salt **101** and contained some functional groups, including a furan ring, to demonstrate the tolerance of these groups in the reaction. The metathesis reaction was effected using a tungsten catalyst, which gave cycloalkyne **102** in a good yield. The synthesis was completed using Lindlar's catalyst to carry out the *Z*-selective hydrogenation (Scheme 23).



Scheme 23: Fürstner's synthesis of the F ring using an alkyne metathesis reaction followed by a Z-selective reduction of the resultant alkyne.

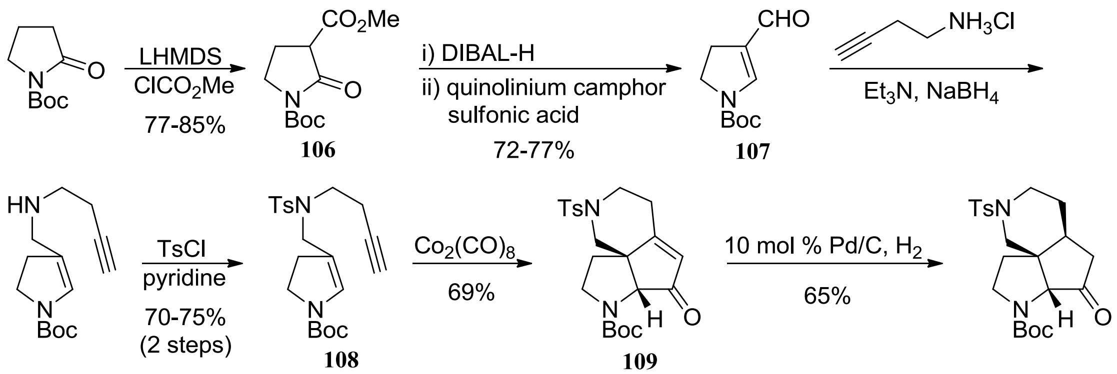
Following this work, the group published the synthesis of the ADE ring structure.[11] A key step from this synthesis was the formation of spirocyclic lactam **103**. Diamide **104** underwent an intramolecular Michael addition, giving **103** as an inseparable mixture of isomeric alkenes. The crude mixture was hydrogenated to give piperidine **105**, which was converted to the ADE ring structure in 7 steps (Scheme 24).



Scheme 24: Fürstner's synthesis of the ADE ring structure.

1.3.5.2. Magnus' approach

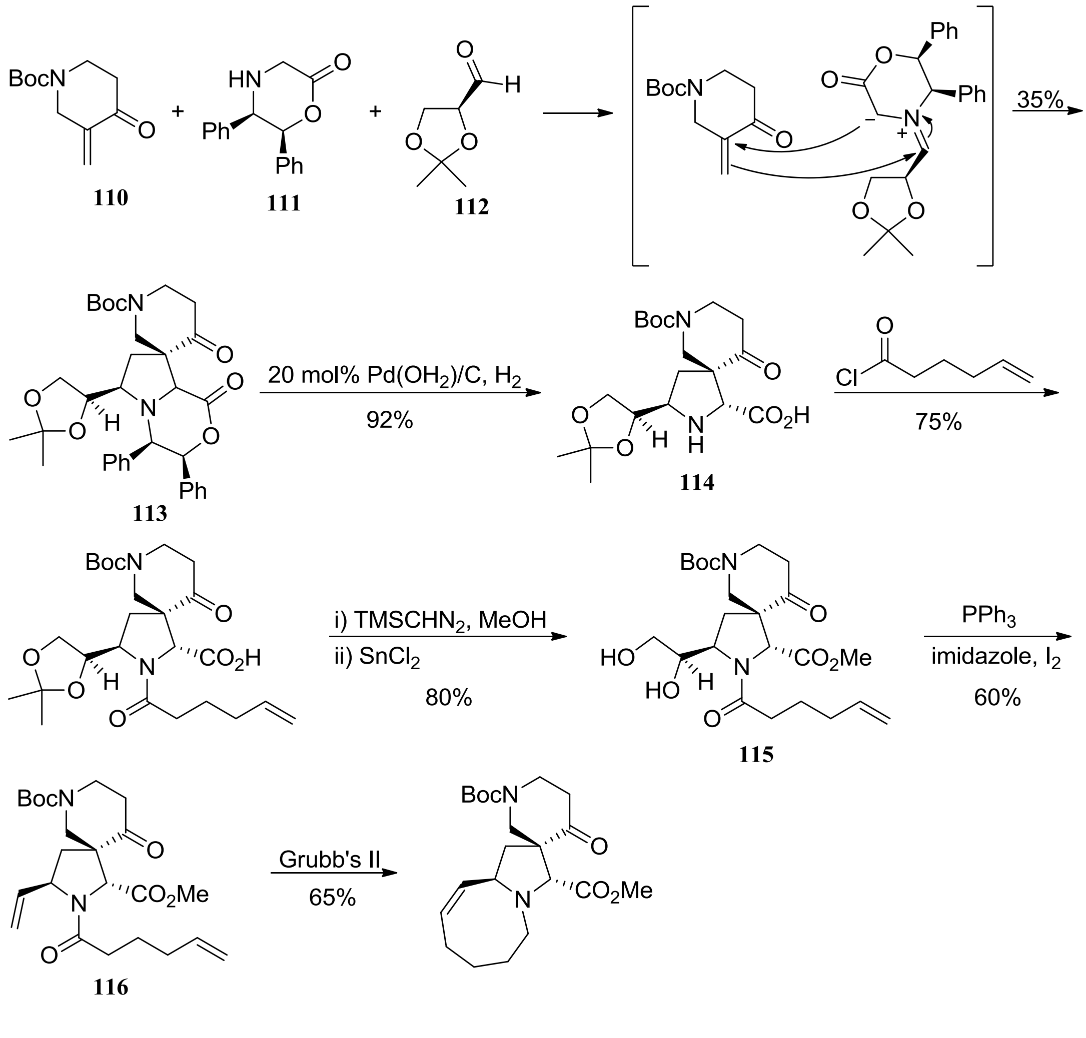
Magnus and co-workers were the first to utilise the Pauson-Khand reaction in their synthetic work on nakadomarin, which was a strategy that was adopted by Mukai and co-workers in their formal synthesis.[26] The synthesis of the Pauson-Khand precursor began with an acylation of *N*-Boc pyrrolidine-2-one using methyl chloroformate to give methyl ester **106**. A partial reduction with DIBAL-H followed by dehydration gave aldehyde **107**. Reductive amination and subsequent tosylation of the secondary amine gave enyne **108**. The Pauson-Khand reaction was carried out using dicobalt octacarbonyl to give tricycle **109**. This was followed by a hydrogenation to give the ABC ring structure (Scheme 25).



Scheme 25: Magnus' approach to the ABC ring structure.

1.3.5.3. Williams' approach

In 2004, the Williams group published a synthesis of the ADE fragment of nakadomarin A in 9 linear steps.[27] The highlight of this synthesis was a 1,3-dipolar cycloaddition of enone **110** with an azomethine ylide formed *in situ* from amine **111** and aldehyde **112**. This reaction allowed the successful synthesis of spirocycle **113** and in the process formed three stereogenic centres, one of which was a quaternary carbon. The cycloaddition was followed by removal of the chiral template to give **114**, which was *N*-acylated with 5-hexenoyl chloride. The resultant amide was treated with trimethylsilyl diazomethane followed by $SnCl_2$, which gave diol **115**. Conversion of the diol functionality gave diene **116** which was subjected to an alkene metathesis reaction using Grubbs' second-generation catalyst, thus forming the ADE ring system of nakadomarin A (Scheme 26).

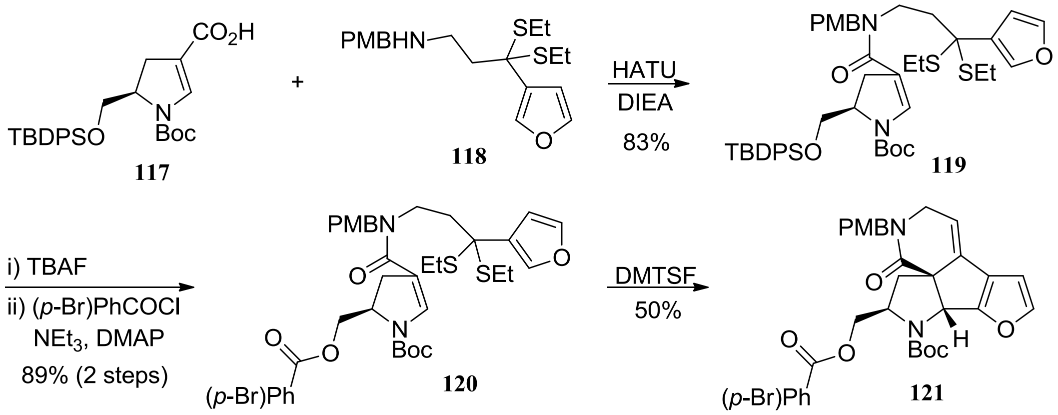


Scheme 26: William's synthesis of the ADE ring system.

1.3.5.4. Winkler's approach

The most recent synthetic approach to nakadomarin A was published by Winkler and co-workers.[28] A similar concept to that of the Funk and Zhai groups was adopted; a vinylogous carbamate would react with an electrophile thus generating an iminium ion, followed by nucleophilic attack of a furan ring to form the central carbocycle and the piperidine ring. This would be achieved through a Pummerer-initiated tandem reaction cascade.

Key steps from Winkler's approach are highlighted in Scheme 27. A coupling reaction of carboxylic acid **117** and *p*-methoxybenzyl amine **118** gave amide **119**, which was followed with a change of protecting group to give **120**. The tandem reaction cascade was initiated with DMTSF which successfully furnished tetracycle **121**.



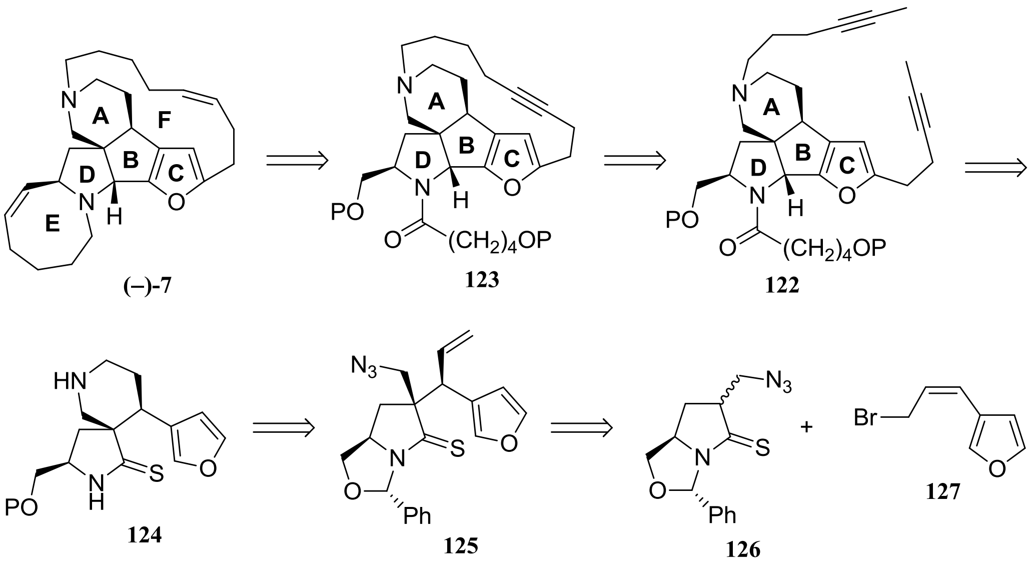
Scheme 27: Cyclisation cascade step from the Winkler approach to nakadomarin A.

1.4. Retrosynthetic analysis

Our strategy for the synthesis of nakadomarin A was to first construct the tetracyclic ABCD ring structure, and follow this with the formation of the E and F rings. The most direct approach to take would be to use RCM reactions to form the two macrocycles, limiting our options to either an alkene or an alkyne metathesis reaction. Alkene RCM reactions to form the E ring are well precedented, however this approach is somewhat inefficient when used to form the F ring, with only the Dixon group obtaining a favourable geometric mixture from the reaction[20]. Alkyne RCM would be used instead, following the work carried out by Fürstner and co-workers.[17]

Disconnection of the E and F rings would give diyne **122**, which also contains two protected alcohol functionalities. A forward synthesis of the E ring from **123** would begin with a removal of the alcohol protecting groups followed by oxidation and Wittig reaction to give a diene, which would be subjected to alkene RCM. The B ring would be formed from **124** *via* furan/iminium ion cyclisation. To construct the A ring, a protocol developed by Evans would be used, which would involve a hydroboration of the terminal alkene of **125** and subsequent cyclisation with concomitant loss of nitrogen.[29]

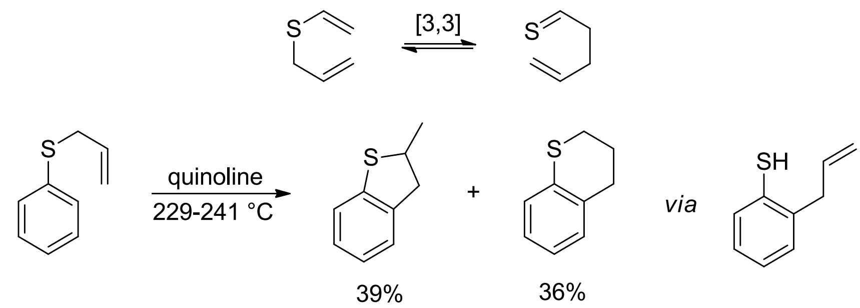
Disconnection of **125** revealed two simpler substrates; bicyclic thiolactam **126** and allylic bromide **127**. Thio-Claisen rearrangement of the two substrates would form the two contiguous stereogenic centres in **125**. The construction of **126** would begin from pyroglutaminol with a benzylidene protection giving the bicyclic skeleton followed by α-alkylation and thionation. Allylic bromide **127** would be formed by a Sonogashira reaction of 3-bromofuran with propargyl alcohol. Subsequent *Z*-selective hydrogenation and bromination would give the desired bromide (Scheme 28).



Scheme 28: Retrosynthetic analysis of nakadomarin A.

1.5. Thio-Claisen rearrangement

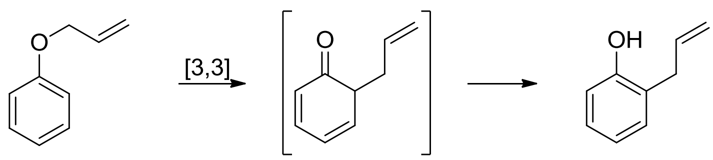
An important component of the synthetic plan is the thio-Claisen rearrangement, which will be used to establish two of the four stereocentres in nakadomarin. The first report of the thio-Claisen rearrangement involved work on an aromatic variant. Kwart *et al*. carried out extensive studies into the sigmatropic rearrangement of allyl phenyl sulfide and found the reaction would proceed *via* *o*-allyl thiophenol to form a mixture of heterocycles (Scheme 29).[30, 31] This section will review this [3,3]-sigmatropic rearrangement and demonstrate in further detail how it will be applied to the synthesis of the natural product.



Scheme 29: This scheme depicts the first report of an aromatic version of the thio-Claisen rearrangement.

1.5.1 Overview of the Claisen rearrangement

The first example of a [3,3]-sigmatropic rearrangement was published by Ludwig Claisen, and involved the rearrangement of allyl phenyl ether to give 2-allyl phenol **128**.[32] Sigmatropic rearrangement gave intermediate **129**, which re-aromatised to give the phenol (Scheme 30).



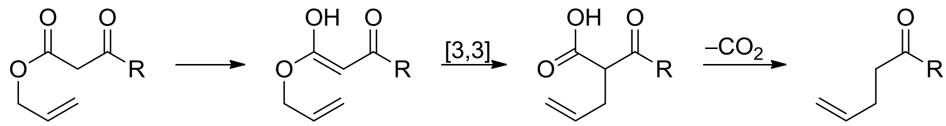
129 **128**

Scheme 30: The first example of a [3,3]-sigmatropic rearrangement.

Since its initial publication, the scope of the Claisen rearrangement has been expanded to include an aliphatic version and is now a widely utilised method for the generation of γ,δ-unsaturated carbonyl compounds. This reaction has undergone significant development since its discovery and aside from the thio-Claisen rearrangement, many other variations now exist, some of which are briefly illustrated in the following section.

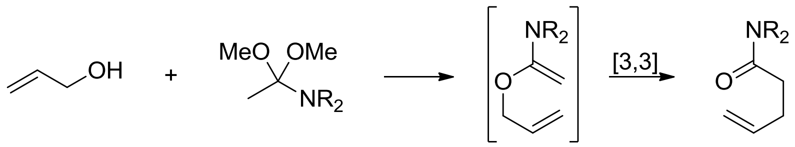
1.5.1.1 Variations of the Claisen rearrangement

The Carroll rearrangement was discovered in 1940 and involves a [3,3]-sigmatropic rearrangement of a β-keto allylic ester to give a β-keto carboxylic acid *via* an intermediate enol.[33-35] The β-keto carboxylic acid undergoes decarboxylation to give a γ,δ-unsaturated ketone (Scheme 31).



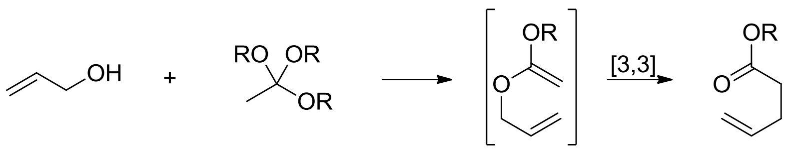
Scheme 31: The Carroll rearrangement.

Following on from work carried out by Meerwein on amide acetals,[36] Eschenmoser *et al*. developed a protocol that allowed for the preparation of γ,δ-unsaturated amides *via* a [3,3]-sigmatropic rearrangement.[37] The reaction involves the formation of an *N*,*O*-acetal from an allylic alcohol and an amide acetal. The resultant *N*,*O*-acetals are not usually isolated, and undergo a subsequent rearrangement to give the unsaturated amide products (Scheme 32).



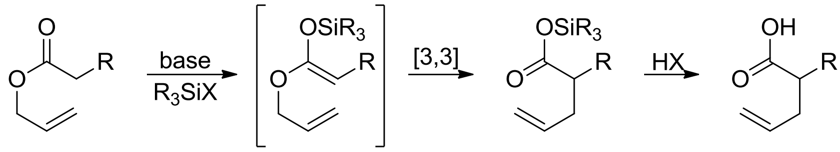
Scheme 32: The Meerwein-Eschenmoser rearrangement.

The Johnson-Claisen rearrangement was first reported in 1970 and involves the sigmatropic rearrangement of an alkyl orthoacetate and an allyl alcohol to give an unsaturated ester.[38] Following the loss of alcohol, a ketene acetal is generated and a subsequent [3,3]-sigmatropic rearrangement affords a γ,δ-unsaturated ester (Scheme 33).



Scheme 33: The Johnson-Claisen rearrangement.

The Ireland-Claisen rearrangement involves the sigmatropic rearrangement of allylic esters *via* ester enolates.[39] The reaction proceeds with the enolisation of an allylic ester by converting the ester to a silyl enol ether. The resultant silyl enol ether undergoes a sigmatropic rearrangement to give γ,δ-unsaturated carboxylic acids (Scheme 34).



Scheme 34: The Ireland-Claisen rearrangement.

1.5.1.2 Mechanism

The mechanism of the Claisen rearrangement involves the migration of a σ-bond with a reorganisation of the π-bonds. The reaction proceeds through either a chair-like or boat-like transition state, both of which are thermally allowed and suprafacial according to the Woodward-Hoffmann rules (Figure 7).[40, 41]

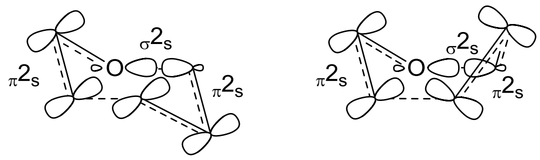
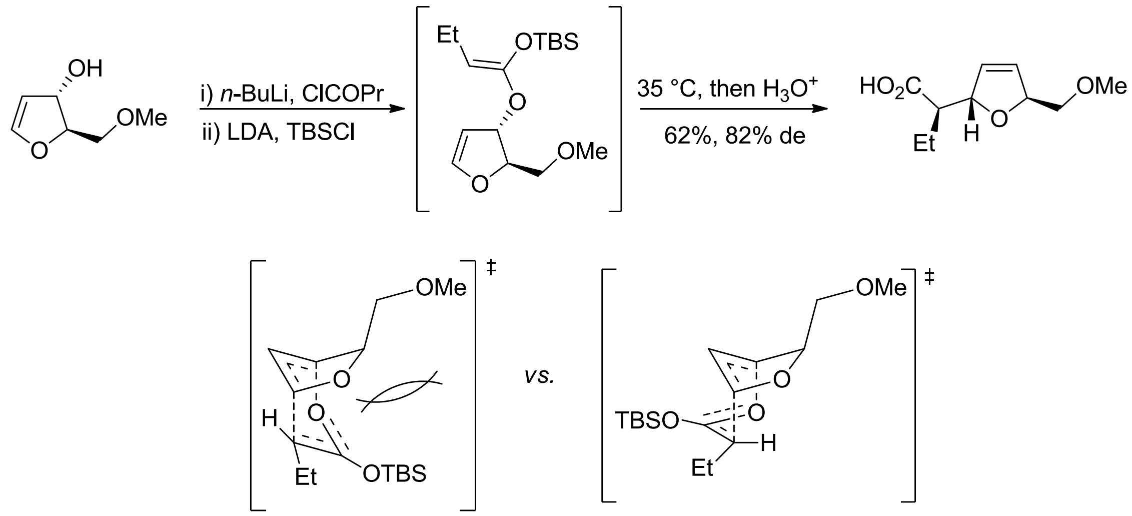


Figure 7: Depiction of the two possible transition states the Claisen rearrangement can proceed through.

The chair-like transition state is usually preferred due to it being lower in energy, however in some cyclic systems a boat conformation may be adopted to alleviate steric strain. Ireland *et al*. demonstrated this through work carried out on the [3,3]-sigmatropic rearrangement of furanoid glycal systems. Although the steric clash between the silyl ether and methyl ether groups in transition state **130** was not perceived to be significant, the product mixture strongly favoured the diastereoisomer arising from boat conformation **131** (Scheme 35).[42, 43]



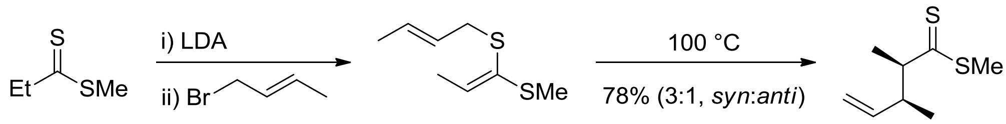
130 **131**

Scheme 35: An example of an Ireland-Claisen rearrangement proceeding through a boat-like transition state.

1.5.2 Distinguishing features of the thio-Claisen rearrangement

The thio-Claisen rearrangement of allyl phenyl sulfide requires higher temperature than its oxygen analogue and leads to mixtures of products. However the aliphatic variant was found to proceed under milder conditions than those required for the rearrangement of aliphatic allyl enol ethers. This could be attributed to the C-S bond being approximately 20 kcal/mol weaker than the C-O bond.

The propensity of the sulfur atom to stabilise a negative charge on itself allows for a relatively facile construction of the thioether rearrangement precursor when compared to the oxygen analogue.[44] α-Deprotonation of a thiocarbonyl group can be achieved with a variety of bases resulting in a thioenolate. The soft nucleophilic nature of the sulfur anion means it is possible to carry out an *S*-alkylation with soft electrophiles such as allyl halides, thus giving the required thioether (Scheme 36).[45]

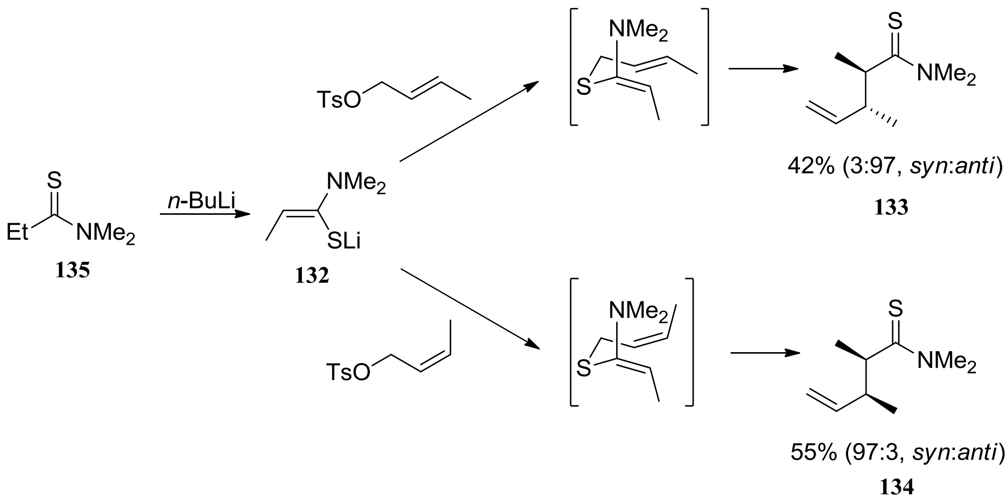


Scheme 36: Example of the synthesis of a thio-Claisen precursor through an *S*-alkylation of a thioenolate.

In the case of thioamides, it is also possible to carry out the alkylation first to give a thioimidate salt and follow this with a deprotonation. The increased acidity of the α-proton following *S*-alkylation means the deprotonation can be effected with relatively weak bases such as tertiary amines. This feature was exploited in work carried out within the group on diastereoselective thio-Claisen rearrangements.[46]

1.5.3 Stereochemical control

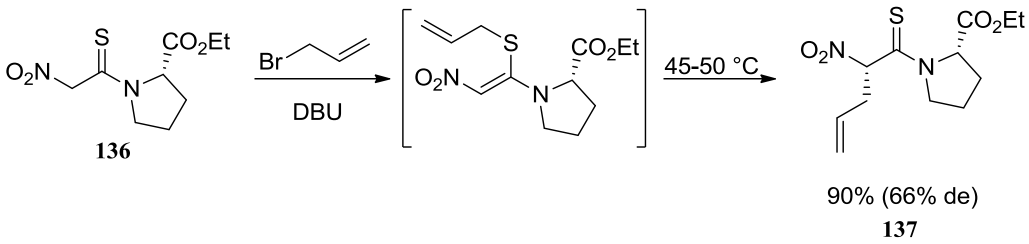
The thio-Claisen rearrangement generally proceeds through a chair-like transition state, which allows for an accurate prediction of the stereochemical outcome of the reaction. Analogous to other [3,3]-sigmatropic rearrangements, the relative stereochemistry can be controlled by varying the alkene geometry in the thioether precursor. Investigations into the relative stereochemistry of the rearrangement were carried out by Yoshida and co-workers (Scheme 37).[47]



Scheme 37: Studies into the relative control observed in the thio-Claisen rearrangement.

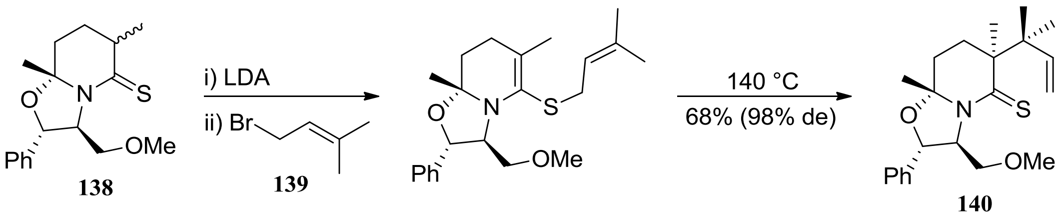
Thioenolate **132** was formed through α-deprotonation using *n*-BuLi. This was followed by alkylation with a *Z* and *E* allyl tosylate. The group reported that when the *Z*-allylic tosylate was used *syn*-diastereoisomer **133** was the major product and in the case of the *E* isomer the reverse was observed, giving almost exclusively *anti*-diastereoisomer **134**. Also noteworthy is the deprotonation of thioamide **135** to give the *Z*-thioenolate. This contrasts with *E*-enolates which are usually formed from carbonyl compounds.[48] Although excellent relative stereochemistry is observed in this rearrangement, the products obtained are racemic. Efforts at developing asymmetric variants of this rearrangement have been reported, which include the use of stereodefined carbon centres in close proximity to the diene and chiral induction from sulfoxide groups.

Chiral auxiliaries have also been used to control the stereochemical outcome of the rearrangement, with the first example published by Reddy who used an L-proline ethyl ester to direct the rearrangement (Scheme 38).[49]



Scheme 38: Use of a chiral auxiliary to control the absolute stereochemistry.

In the example shown above, the allylation of nitrothioacetamide **136** was carried out using allyl bromide and DBU to give an *N*,*S*-acetal which was heated to give rearranged product **137**. The moderate stereocontrol obtained could have been attributed to the free rotation around the C-N bond. A more stereoselective thio-Claisen reaction was reported by Meyers.[50] The cyclic chiral auxiliary was replaced with a stereodefined fused bicyclic ring system (Scheme 39). The rigid bicyclic framework in **138** prevented rotation around the C-N bond, which improved facial selectivity and therefore led to an increase in the stereoselectivity of the rearrangement.

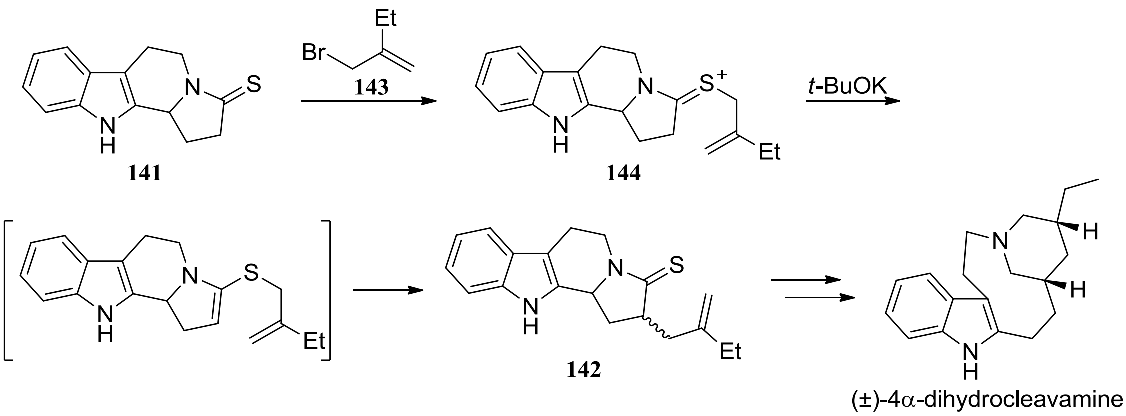


Scheme 39: Chiral induction from a fused bicyclic oxazolidine.

In the example illustrated above, the deprotonation is carried out using LDA, followed by *S*-alkylation with allylic bromide **139** to give **140** with a diastereomeric excess of 98%, a marked increase over the example shown in Scheme 38.

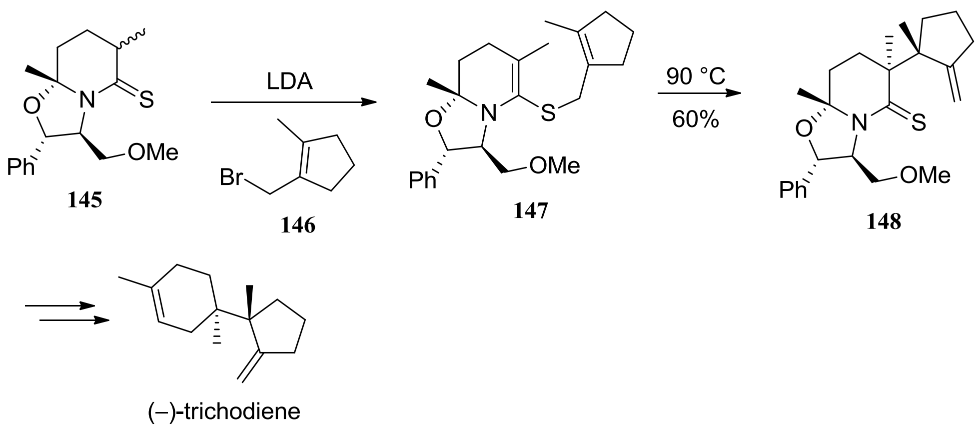
1.5.4 Synthetic applications

The benefits of the thio-Claisen rearrangement are clear; it is an efficient protocol in the synthesis of C-C bonds and allows for predictable and highly effective stereocontrol. However examples of its use in synthesis are scarce. One of the first groups to recognise the potential of the thio-Claisen rearrangement was that of Takano, applying it to total syntheses of (±)-4α-dihydrocleavamine and (±) quebrachamine.[51] The example below shows the thio-Claisen rearrangement of thioamide **141** to construct adduct **142**, in the synthesis of (±)-4α-dihydrocleavamine (Scheme 40). Thioamide **141** was allylated with allylic bromide **143** to give thioimidate salt **144**. Deprotonation was carried out with *t*-BuOK followed by spontaneous rearrangement to give **142**, which was subsequently converted to the natural product.



Scheme 40: Thio-Claisen rearrangement from Takano's synthesis of (±)-4α-dihydrocleavamine.

The Meyers group applied the asymmetric thio-Claisen rearrangement protocol they had developed earlier to the synthesis of (−)-trichodiene (Scheme 41).[52] Thioamide **145**, which was also used in their early studies on the rearrangement, was deprotonated with LDA, which was followed with allylation with allylic bromide **146** to give *N*,*S*-ketene acetal **147**. After extensive optimisation, the most favourable result was obtained when **147** was heated in DMF to give thioamide **148** as a single diastereoisomer and starting material **145**. Thioamide **145** was resubmitted to the reaction and yielded a further 10% of **148**. Following the synthesis of **148**, the natural product was constructed in 4 steps.

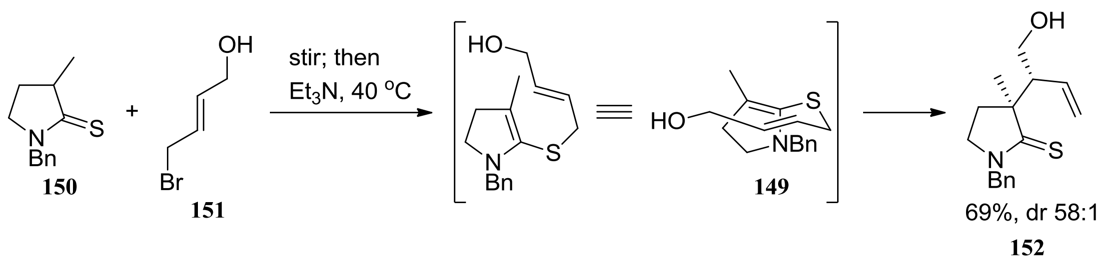


Scheme 41: Thio-Claisen rearrangement from Meyers' synthesis of (−)-trichodiene.

As demonstrated by Meyers, excellent stereochemistry in the thio-Claisen rearrangement can be achieved when using a stereodefined bicyclic ring system. This prompted us to adopt a similar strategy in the synthesis of nakadomarin A as highlighted in the retrosynthetic plan.

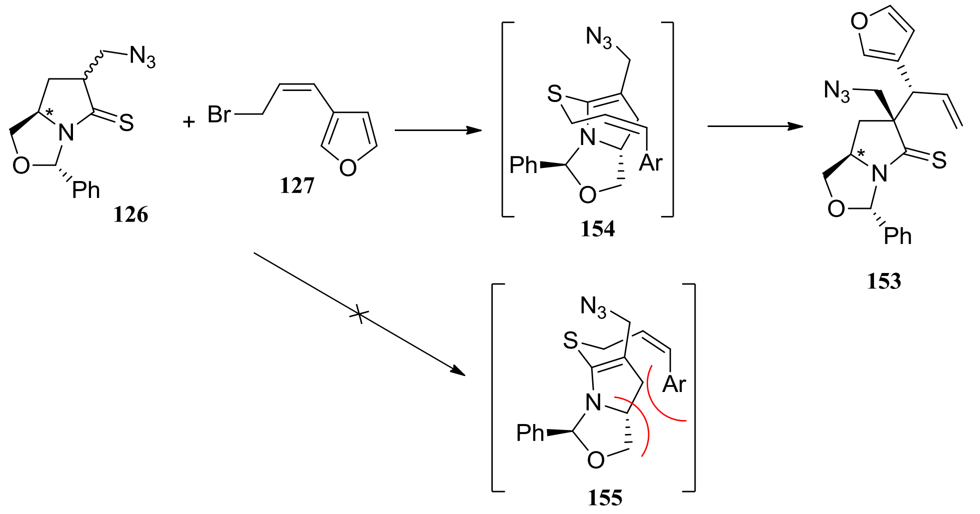
1.5.5 Previous work and application to the synthesis of nakadomarin

Previous work in the Porter group has led to an efficient and highly stereoselective preparation of functionalised pyrrolidinethiones through a thio-Claisen rearrangement (Scheme 42.[46] The chair transition state **149**, which is formed through an *S*-allylation of thioamide **150** with allylic bromide **151** followed by deprotonation, gave primarily the diastereoisomer **152**, although as a racemic mixture.



Scheme 42: Previous work in the Porter group on the thio-Claisen rearrangement.

The scheme below shows how this protocol will be used in our synthesis to obtain **153** as a single diastereoisomer (Scheme 43). The chair transition state arising from the use of *Z*-allylic bromide **127** should give the correct relative stereochemistry in **123**; in addition, the introduction of the stereodefined group highlighted in **126** should favour chair transition state **154** over **155**, giving diastereomer **153** as the major product.

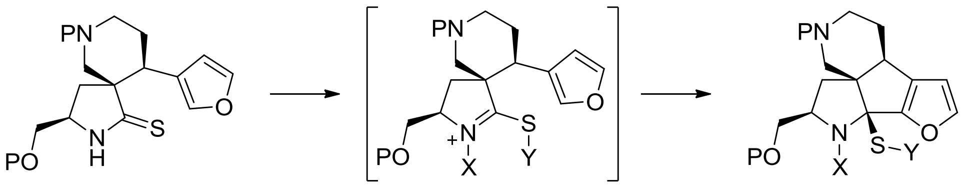


Scheme 43: Application of the thio-Claisen rearrangement to form two stereogenic centres.

2. RESULTS AND DISCUSSION

2.1. Development of a furan-iminium cyclisation

As outlined in the introduction, a key component of the synthetic plan involves the cyclisation of a furan ring onto an iminium ion to form the carbocyclic B ring. As the plan also includes the use of a thio-Claisen rearrangement to establish the correct stereochemical configuration, an iminium ion would have to be derived from a thioamide group. The proposed strategy is illustrated in Scheme 44. The thioamide functionality of compound **156** could be converted by alkylation or acylation of the nitrogen and sulfur atoms to iminium ion **157**, which could then undergo nucleophilic attack from the furan ring to form the desired carbocycle of **158**.

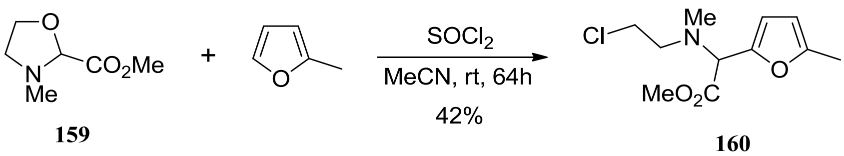


156 **157** **158**

Scheme 44: Proposed formation of the nakadomarin B-ring via conversion of the thioamide group to an iminium ion.

2.1.1. Cyclisation of a furan onto a *C*-sulfanyliminium ion

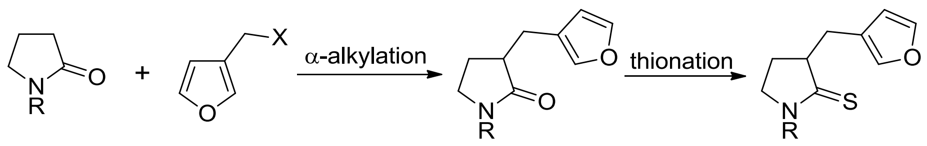
Several groups have previously shown that furans can undergo nucleophilic reactions with iminium ions.[53-59] For example, Heaney *et al*. have shown that cyclic hemiaminal ether **159** can be converted to an iminium ion *via* an $SOCl_2$ mediated ring opening.[60] The resultant electrophile is then trapped with 2-methylfuran to give compound **160** (Scheme 45).



159 **160**

Scheme 45: Reaction of an iminium ion generated from **159** with 2-methylfuran to give **160**.

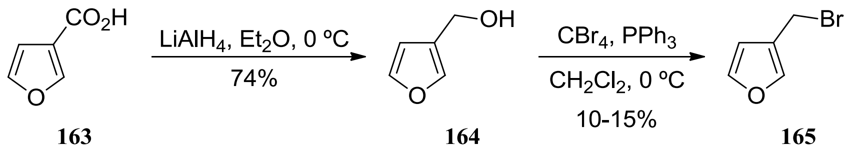
Although this type of reaction is well documented, there is a lack of precedent in cyclising a furan ring onto an iminium ion bearing a sulfur substituent. This was therefore chosen as the starting point of our investigations, which began with the construction of a model system to test the proposed transformation in Scheme 44. Alkylation of *N*-alkylated pyrrolidin-2-one **161** followed by thionation would give cyclisation precursor **162** (Scheme 46).



161 **162**

Scheme 46: Proposed strategy to the thiolactam cyclisation precursor.

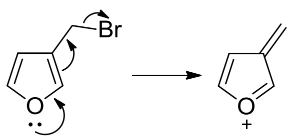
Work commenced with the synthesis of a suitable alkylating agent. 3-Furoic acid **163** was reduced using $LiAlH_4$ to give alcohol **164** which was brominated using CBr_4/PPh_3 to give the desired bromide **165** in a poor yield (Scheme 47).



163 **164** **165**

Scheme 47: Synthesis of bromide **165**.

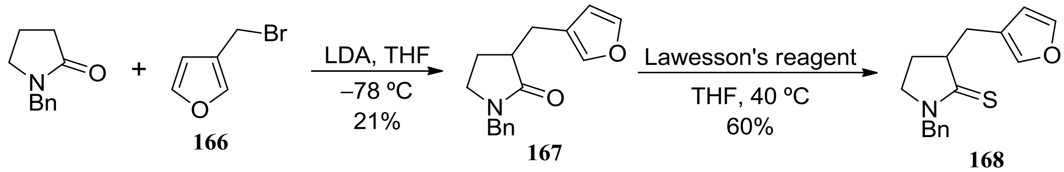
The low yield obtained from the bromination may be attributable to the lability of the product. The ability of the bromide to function as a good leaving group along with the inherent electron rich nature of the furan ring could eject the bromide to give stabilised cation **166** (Scheme 48).



165 **166**

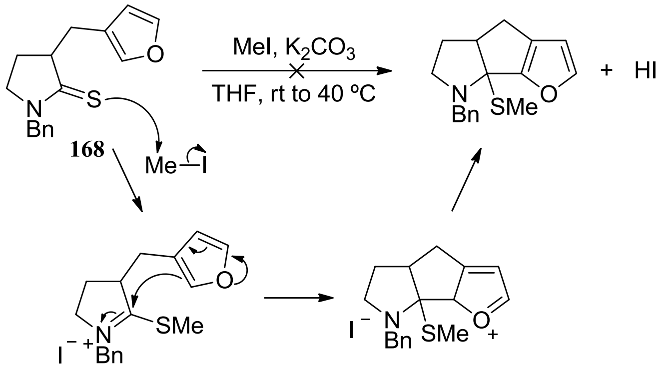
Scheme 48: Decomposition of bromide **165** through the loss of a bromide ion.

Nevertheless, the bromide was used to alkylate *N*-benzylpyrrolidin-2-one with LDA used as base to give lactam **167**. This in turn was converted to compound **168** using Lawesson's reagent to thionate the amide moiety (Scheme 49).[61]



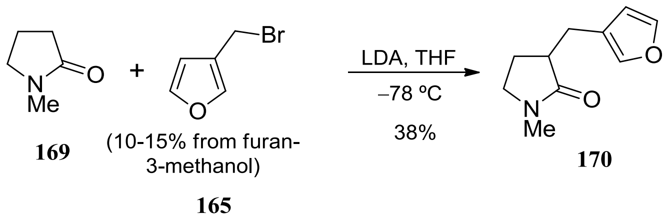
Scheme 49: Synthesis of thiolactam **168**.

With the successful synthesis of the cyclisation precursor, our attention turned to the furan cyclisation. The 'soft' nucleophilic nature of the sulfur suggested that alkylation of the thiolactam was a possible method to generate the *C*-sulfanyliminium ion. Iodomethane was selected as the alkylating agent, with K_2CO_3 added to neutralise the HI which would be formed upon cyclisation (Scheme 50)



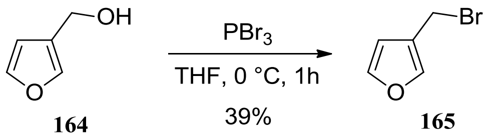
Scheme 50: Proposed MeI mediated cyclisation.

The alkylation-cyclisation sequence was attempted in THF, initially at room temperature and then at 40 ºC, however due to the overlap of benzyl and furyl peaks in the ^{1}H NMR spectrum it was difficult to determine whether cyclisation had taken place and so a second substrate was prepared with an *N*-methyl in place of an *N*-benzyl group (Scheme 51).



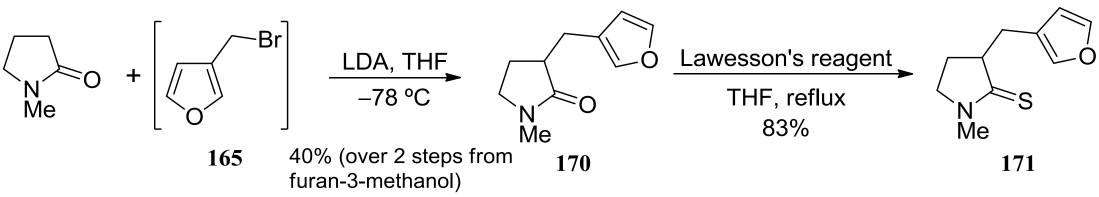
Scheme 51: Alkylation of lactam **169** with bromide **165**.

The desired lactam was successfully synthesised, however the low yields in both the formation of bromide **165** and the alkylation of **169** prompted us to optimise this sequence. A number of methods for preparation of a suitable alkylating agent were investigated. Use of NBS/PPh_3[62] led only to bromination of the furan ring, while attempts to form the corresponding tosylate[63] led to significant decomposition. The most successful method investigated was the use of PBr_3, which gave the desired bromide **165** in 39% yield (Scheme 52).[64]



Scheme 52: Bromination of alcohol **164** with PBr_3.

Although the yield from PBr_3 was higher than that from CBr_4/PPh_3, it was still low and we considered that isolation of the product may be the cause of the problem. To circumvent this, the bromination and alkylation steps were carried out without isolation of the intermediate bromide **165**. The bromide was synthesised using PBr_3, then used immediately as a solution in THF. This approach gave lactam **170** in a moderate yield of 40% over 2 steps from alcohol **164**. The lactam was thionated using Lawesson's reagent thereby giving *N*-methylated cyclisation precursor **171** (Scheme 53).

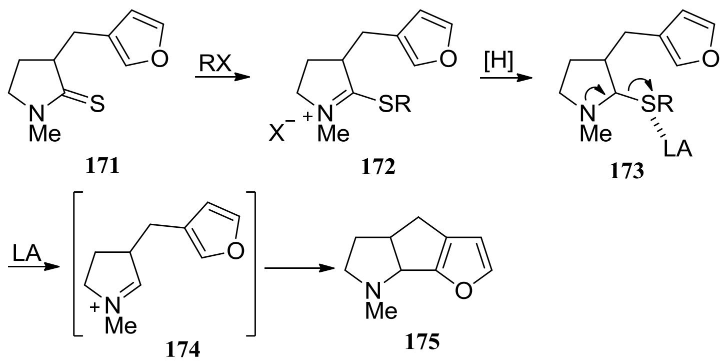


Scheme 53: Synthesis of thiolactam **171**.

The cyclisation of the *N*-methylated thiolactam was attempted using MeI and K_2CO_3 in THF at room temperature and at 40 ºC, however no reaction was observed. The reaction was repeated in MeCN at both ambient temperature and 40 ºC, which again led to no reaction. This strategy was therefore abandoned and we continued our research by looking at other methods to form the B ring of nakadomarin A.

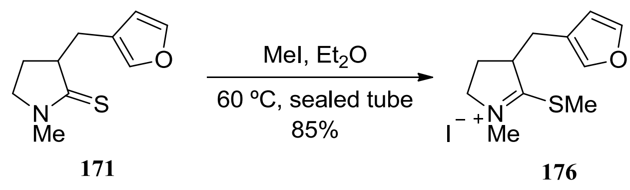
2.1.2. Reduction of a *C*-sulfanyliminium salt

We considered that the failure of the cyclisations in the previous section may have been due to the deactivating effect of the sulfur substituent on the iminium ion and therefore decided to look for ways of converting a thioamide to an iminium ion without the sulfur. There are many examples of the formation of iminium ions through the dehydration of hemiaminal groups under acidic conditions. Indeed, this approach was successfully utilised by the Dixon group in their synthesis of nakadomarin. We planned to generate *C*-sulfanyliminium salt **172** and to reduce it to *N*,*S*-acetal **173**. Treatment with a thiophilic Lewis acid should generate iminium ion **174** which could react with the furan ring to give tricycle **175** (Scheme 54).



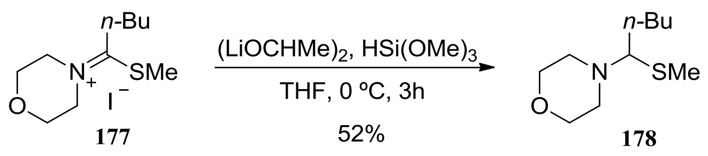
Scheme 54: Proposed reduction of a *C*-sulfanyliminium ion followed by iminium ion generation.

Alkylation of the thiolactam **171** was carried out with MeI in Et_2O. The reaction mixture was heated to 60 ºC in a sealed tube, and salt **176** precipitated out in 85% yield (Scheme 55).



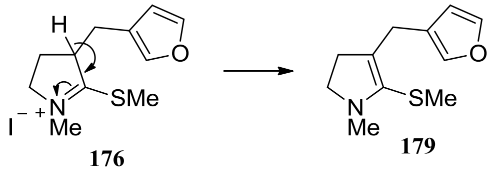
Scheme 55: Methylation of thiolactam **171** to give a *C*-sulfanyliminium salt

The *C*-sulfanyliminium salt reduction was first attempted using chemistry developed by the group of Hosomi,[65] who had shown that *C*-sulfanyliminium iodides are reduced by trimethoxysilane in the presence of dilithium-2,3-butanediolate (Scheme 56).



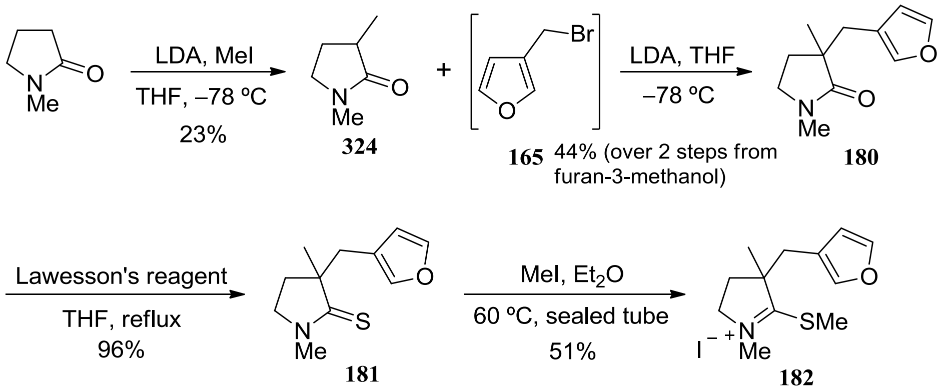
Scheme 56: Reduction of *C*-sulfanyliminium iodide **177** to thioether **178** using $(LiOCHMe)_2/HSi(OMe)_3$.

It is believed that a pentacoordinate silicon hydride species formed in the reaction is responsible for the reduction of the iminium salts.[66] Unfortunately, our attempts to reduce salt **176**, either under Hosomi's conditions or using $NaBH_4$ in MeOH, were unsuccessful. Significant solubility problems were encountered with the iodide salt, which may have been responsible for the unsuccessful reactions. We felt that another potential problem in these reductions was the formation of an *N*,*S*-ketene acetal through deprotonation of the iminium salt (Scheme 57).



Scheme 57: Loss of acidic proton in iminium salt **176** to give *N*,*S*-ketene acetal **179**.

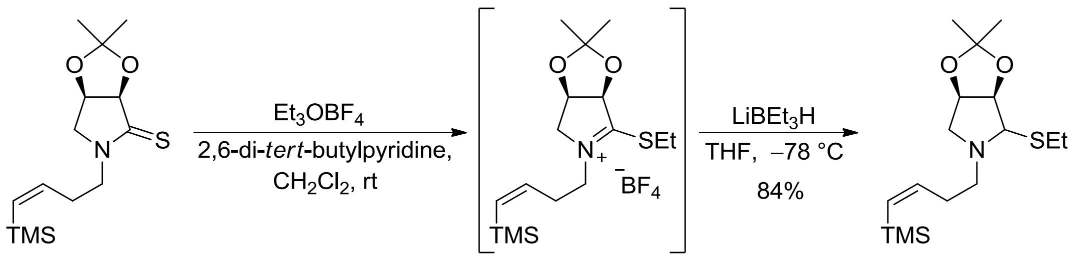
The model system was re-synthesised with a methyl group α to the C-S bond to remove the acidic proton (Scheme 58). The synthesis began with sequential alkylations of *N*-methylpyrrolidin-2-one with MeI and bromide **165** to give lactam **180**, with bromide **165** used as a solution in THF giving a good yield over 2 steps. Thionation of lactam **180** using Lawesson's reagent gave thiolactam **181** which was subsequently methylated with MeI to give desired iodide salt **182**.



Scheme 58: Synthesis of *C*-sulfanyliminium iodide salt **182**.

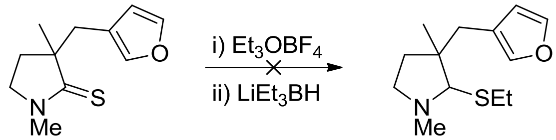
With the successful synthesis of iodide salt **182**, we were able to continue with our studies into the reduction of *C*-sulfanyliminium ion substrates. The reduction was attempted using triethoxysilane, however the iodide salt had limited solubility in THF and hydrolysed to lactam **180** upon work-up. Following this result more conventional reducing agents were investigated. The reduction was attempted with Super Hydride® and $NaBH_3CN$ and in both cases the starting *C*-sulfanyliminium salt was obtained.

Thus far, the problem in establishing reduction conditions for salt **182** was its limited solubility in most solvents. A change of the counter ion of the salt could alter its solubility characteristics and thereby overcome this problem. Overman *et al.* have investigated the generation of a *C*-sulfanyliminium ion from a thioamide using Meerwein's salt, giving a salt with a BF_4^- counter-ion, which can be reduced using Super Hydride® giving the desired ethyl thioether (Scheme 59).[67]



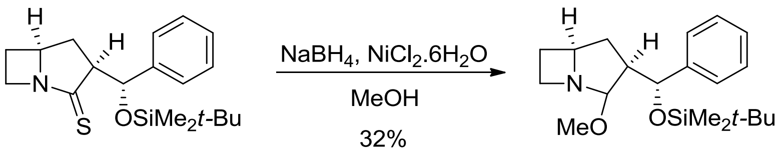
Scheme 59: An example of work carried out by Overman involving the synthesis of a C-sulfanyliminium salt followed by a reduction using Super Hydride®.

However, when the alkylation/reduction of thiolactam **181** was carried out under these conditions, only starting thiolactam was recovered (Scheme 60).



Scheme 60: Attempted synthesis of a sulfide using a procedure developed by Overman and co-workers.

As we were having limited success with the reduction of the *C*-sulfanyliminium ion, other possibilities that deviated slightly from the original strategy were considered. Barrett *et al*. reported that $NiCl_2/NaBH_4$ can be used to convert a thiolactam to a hemiaminal ether, which can be readily converted to an iminium ion (Scheme 61).[68]



Scheme 61: Work reported by Barrett and co-workers involving the conversion of a thioamide to a hemiaminal ether.

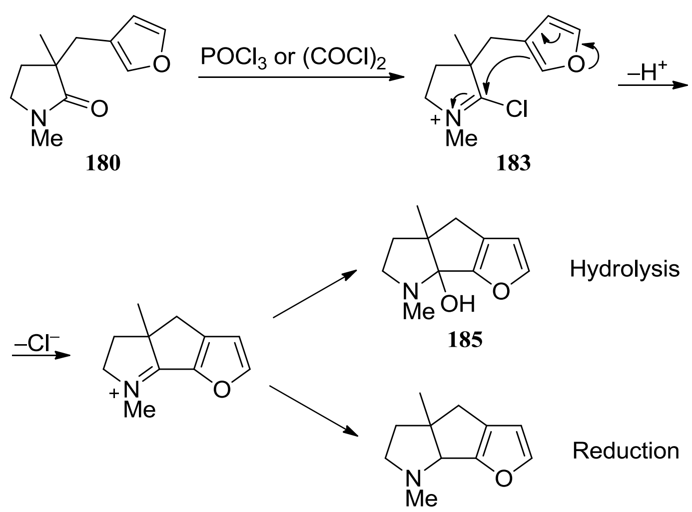
These conditions were used in an attempt to reduce thiolactam **181**, but a complex product mixture was obtained. The lack of methyl peaks with chemical shifts above 3 ppm in the ^{1}H NMR spectrum suggested the absence of the hemiaminal ether product. However several singlet peaks with a chemical shift range of 2.2-2.7 ppm were observed, possibly indicating the presence of the *N*-methylamine product arising from desulfurisation of **181**, along with other unidentified products.

2.1.3. Generation of a chloroiminium ion

We presumed that the predominant problem with previous attempts at this cyclisation had been the low solubility of the *C*-sulfanyliminium iodide. It was also envisaged that the presence of an electron donating sulfur substituent could decrease its electrophilicity, thus preventing the cyclisation of the furan ring.

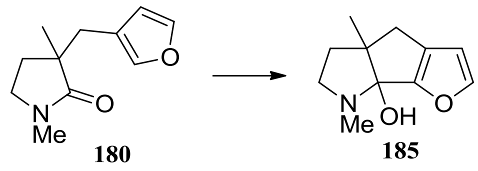
The substitution of electron-rich arenes with formyl groups *via* a Vilsmeier reaction is well documented and there are many examples of furan rings undergoing this reaction.[69-71] The mechanism involves the formation of the Vilsmeier reagent, a chloro-iminium ion, through the reaction of DMF with $POCl_3$ or $(COCl)_2$. This is followed by an electrophilic aromatic substitution and subsequent hydrolysis to give the formylated arene.

The next strategy investigated was thus to convert a lactam precursor to a chloroiminium electrophile. As a chloroiminium ion would be more electrophilic than the *C*-sulfanyliminium ion, it should undergo nucleophilic attack from the furan ring more readily. The enhanced electrophilicity of a chloroiminium ion is due to the inductive effect of the electronegative chloride. Scheme 62 shows the application of this protocol using lactam **180**. Vilsmeier intermediate **183** would be generated by reacting lactam **180** with $POCl_3$ (oxalyl chloride could also be used). This could then undergo attack from the furan ring followed by a re-aromatisation to give tricycle **184**, which would then be hydrated on work-up to give hemiaminal **185**. Alternatively, it may prove possible to reduce the iminium ion *in situ* to give the fully reduced product.



Scheme 62: Proposed iminium ion-furan cyclisation through the formation of a Vilsmeier intermediate.

Investigation of this protocol began with $POCl_3$ and $(COCl)_2$ used to generate the chloroiminium ion in CH_2Cl_2 at 0 °C (entries 1 and 2, Table 1). Both attempts were unsuccessful and increasing the amount of $(COCl)_2$ gave a complex mixture. The reactions were repeated in MeCN and heated to reflux, however these met with failure, with $(COCl)_2$ giving a complex mixture. No significant decomposition was observed using $POCl_3$,[72] therefore the cyclisation was repeated using neat $POCl_3$ in refluxing conditions. To our surprise, the starting lactam was recovered with no significant decomposition. The cyclisation was also attempted with TFAA with no success. It was possible that lactam **180** underwent conversion to the chloroiminium ion and hydrolysed to the lactam upon work-up before cyclisation of the furan ring could take place.

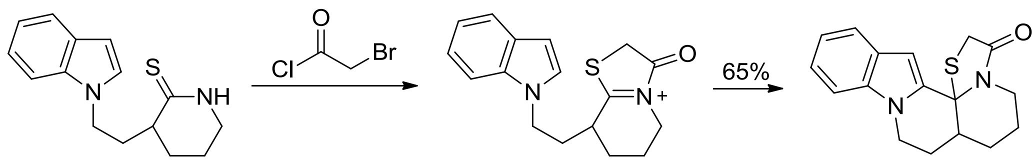


Entry	Conditions	Yield%
1	$POCl_3$ (1.2eq), CH_2Cl_2, 0 °C	0[a]
2	$(COCl)_2$ (1.2eq), CH_2Cl_2, 0 °C	0[a]
3	$(COCl)_2$ (10eq), CH_2Cl_2, 0 °C	0[b]
4	$(COCl)_2$ (1.2eq), MeCN, reflux	0[a]
5	$POCl_3$ (1.2eq), MeCN, reflux	0[b]
6	$POCl_3$ (neat), reflux	0[a]
7	TFAA (1.2eq), pyridine, dioxane 0 °C	0[a]
[a] no reaction, starting material obtained; [b] complex mixture obtained		

Table 1: Attempts at a furan-chloroiminium ion cyclisation.

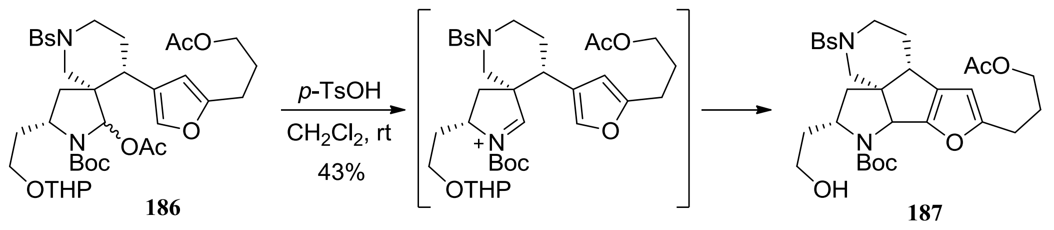
2.1.4. Generation of an iminium ion *via S*-alkylation and *N*-acylation

Padwa *et al*. have shown that iminium ions can be generated through a sequential *S*-alkylation and *N*-acylation of secondary thioamide groups with bromoacetyl chlorides.[73, 74] These *N*-acyliminium ions can undergo intramolecular attack from various nucleophiles including internal alkenes, methoxybenzyl groups and indole rings as shown in Scheme 63, to give *N*,*S*-acetals.



Scheme 63: The generation of a thio-*N*-acyliminium ion through a sequential *S*-alkylation and *N*-acylation. This then undergoes nucleophilic attack from an indole.

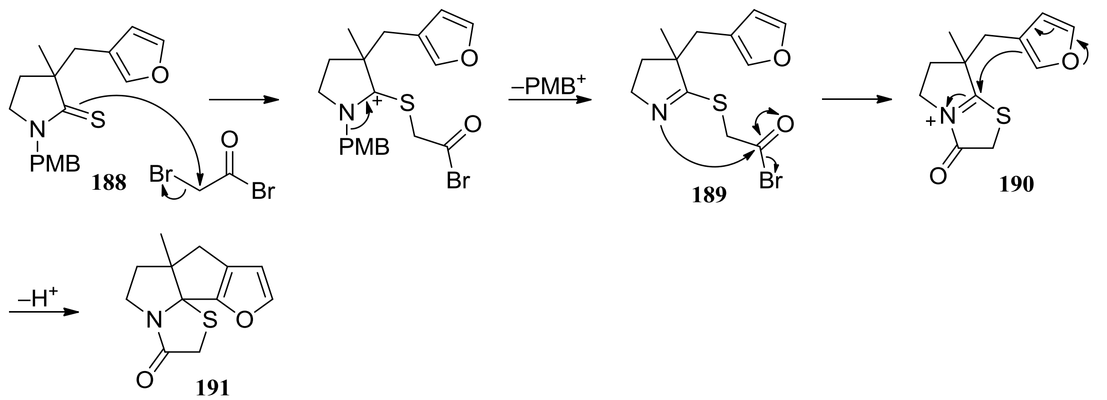
The iminium ions generated through this protocol are strongly electrophilic due to the electron withdrawing acyl group on the nitrogen atom.[75] Cyclisation of a furan onto an *N*-acyliminium ion has been used as a key step in several of the literature syntheses of nakadomarin A.[18, 23, 76] The example in Scheme 64 taken from Nishida's synthesis shows the generation of an *N*-acyliminium ion from acetate **186** followed by cyclisation to give tetracycle **187**.[10]



Scheme 64: An example from Nishida's synthesis of the generation of an *N*-acyliminium ion followed by a cyclisation of the furan ring to give the tetracyclic ring structure of (+)-**7**.

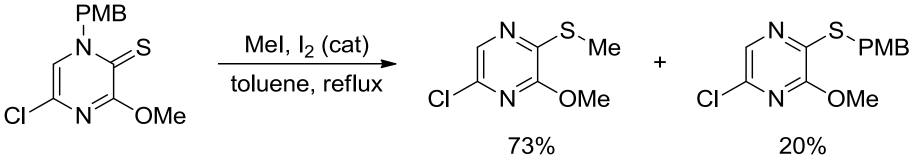
2.1.4.1. One-pot PMB group deprotection/cyclisation

To determine whether a furan ring could cyclise onto a *C*-sulfanyliminium ion, it was decided to test this reaction on a model substrate, a PMB protected thiolactam. Alkylation of thiolactam **188** with a bromoacetyl bromide followed by loss of PMB cation could give thioimidate **189**. Intramolecular acylation should furnish *C*-sulfanyliminium ion **190**, which would be followed by cyclisation of the furan ring to give tetracycle **191** (Scheme 65).



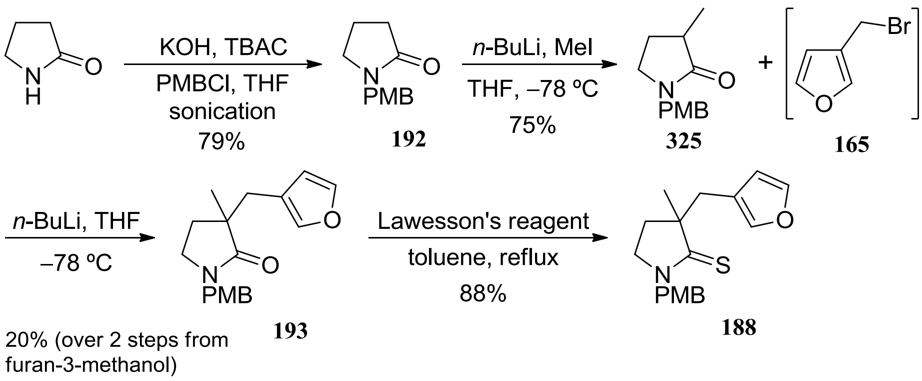
Scheme 65: Revised strategy showing a one-pot PMB group deprotection/furan cyclisation.

A limitation of Padwa's approach is that it requires the use of an unprotected thioamide group, which could lengthen our synthesis by having to introduce additional protection/deprotection steps. To avoid these additional steps, we first investigated an approach in which a nitrogen protecting group would be removed during the *S*-alkylation step. The proposed approach in Scheme 65 differs from Padwa's approach in that it incorporates a removal of the PMB protecting group following *S*-alkylation. Van der Eycken *et al*. have shown that PMB protected pyrazine-thiones can be deprotected through alkylation of thioamide groups with MeI to form thioethers (Scheme 66).[77]



Scheme 66: *In situ S*-methylation PMB group deprotection.

Synthesis of the model system began with a PMB protection of pyrrolidin-2-one using PMBCl with sonication, giving lactam **192** (Scheme 67). Sequential alkylations with MeI and bromomethyl furan **165** using *n*-BuLi as base gave lactam **193**. This was thionated with Lawesson's reagent to give thiolactam **188**, and thus successfully giving the cyclisation precursor.



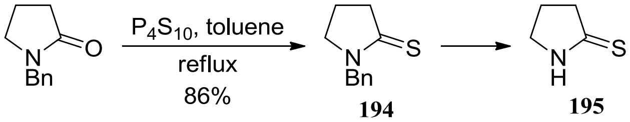
Scheme 67: Synthesis of a model system containing a PMB protected thiolactam.

The cyclisation was attempted using bromoacetyl bromide in toluene and heated to reflux, however the reaction was unsuccessful and the starting thiolactam was recovered. The reaction was repeated with the addition of thioanisole, a cation scavenger, and was also unsuccessful. The example taken from the work of Van der Eycken in Scheme 66 suggests that re-aromatisation to give the pyrazine may be the driving force behind the deprotection of the thioamide group.

2.1.4.2. Deprotection of a benzyl protected thiolactam

The sequential PMB deprotection/cyclisation had been unsuccessful and so it was decided that the approach taken by the Padwa group would be followed, with the use of an unprotected thiolactam.

The synthesis of the unprotected thiolactam would be tackled in a similar way to the synthesis of previous model systems, with sequential alkylations to install the methyl group and the furan ring. This required protection of the starting pyrrolidine-2-one to eliminate *N*-alkylation by-products. Deprotection of benzyl protected lactams is well documented and is usually carried out by a dissolving metal reduction to reductively cleave the benzyl group.[78, 79] However, there is little precedent for the deprotection of *N*-benzylated thiolactams and so it was decided to test this deprotection on a simple benzyl protected thiolactam. Thiolactam **194** was prepared from *N*-benzylpyrrolidin-2-one using P_4S_{10} and several dissolving metal reductions were attempted (Table 2).



194 **195**

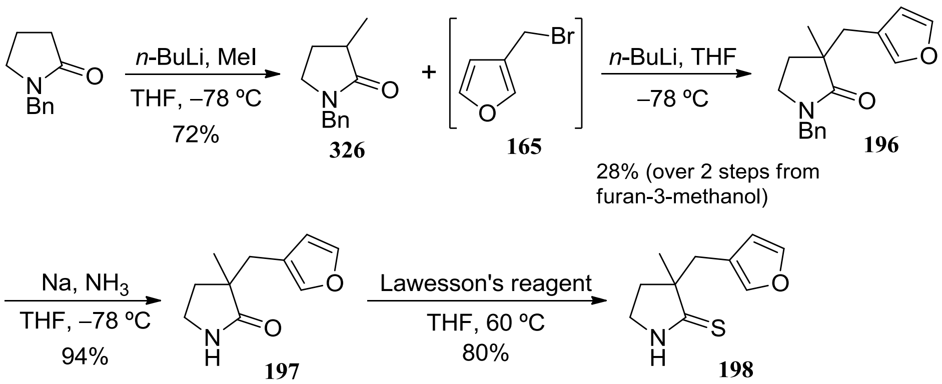
Entry	Conditions	Conversion%
1	Li (3 eq), NH_3, THF, –78 °C	0[a]
2	Li (5 eq), naphthalene (5 eq), THF, 0 °C	20[b]
3	Li (3 eq), di-*t*-butylbiphenyl (5 eq) THF, –78 °C	60[b]
[a] no reaction, [b] percentage conversion determined by ^{1}H NMR analysis of the crude product.		

Table 2: Attempted debenzylation of thiolactam **194** using a dissolving metal reduction.

Entry 1 shows the reduction attempted with standard Birch reduction conditions, which were unsuccessful in deprotecting the thiolactam. The reduction was then attempted with lithium napthalenide, which was formed *in situ* from lithium and naphthalene giving a deep blue solution upon formation of the active electron carrier.[80] The crude product was analysed by ^{1}H NMR analysis and showed *ca*. 4:1 ratio of **194** to **195**. This increased to *ca*. 2:3 ratio in favour of the unprotected thiolactam when LDBB, formed *in situ* from lithium and 4,4-di-*tert*-butylbiphenyl, was used.[81] This strategy was abandoned due to difficulties in getting the reaction to go to completion.

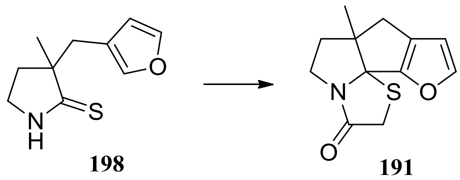
2.1.4.3. Furan-iminium ion cyclisation of an unprotected thiolactam

As a result of the difficulties encountered with the deprotection of the *N*-benzylated thiolactam, the debenzylation would be carried out before conversion to the thiolactam in the synthesis of the model system. Construction of the unprotected thiolactam began with the double alkylation of *N*-benzylpyrrolidin-2-one with MeI followed by bromide **165**. The resulting lactam **196** was deprotected using Birch reduction conditions. The reaction rapidly gave the desired amide **197** in an almost quantitative yield. Thionation with Lawesson's reagent gave secondary thiolactam **198** (Scheme 68).



Scheme 68: Synthesis of a model system containing an unprotected thioamide group.

The initial attempt at the cyclisation of **198** was carried out using Padwa's conditions; bromoacetyl chloride and NEt_3 in toluene followed by heating to reflux (Table 3, entry 1). Pleasingly, we successfully synthesised the desired tetracycle, albeit in a low yield. A potential side reaction between NEt_3 and bromoacetyl chloride could have contributed to the low yield. Thus the reaction was repeated with the omission of the base, which increased the yield further to 53%. The last entry shows an attempt at the cyclisation using methyl bromoacetate. The advantage of using this over an acyl chloride is that the by-product is MeOH. The reaction was carried out in a sealed tube and after heating for 18 h gave tetracycle **191** in a yield of 73%.



198 191

Entry	Conditions	Yield%
1	Bromoacetyl chloride (1.2 eq), NEt_3 (3 eq), toluene, reflux, 2 h	26
2	Bromoacetyl chloride (1.1 eq), toluene, 100 °C, 2 h	53
3	Methyl bromoacetate (1.2 eq), toluene, sealed tube, 150 °C, 18 h	73

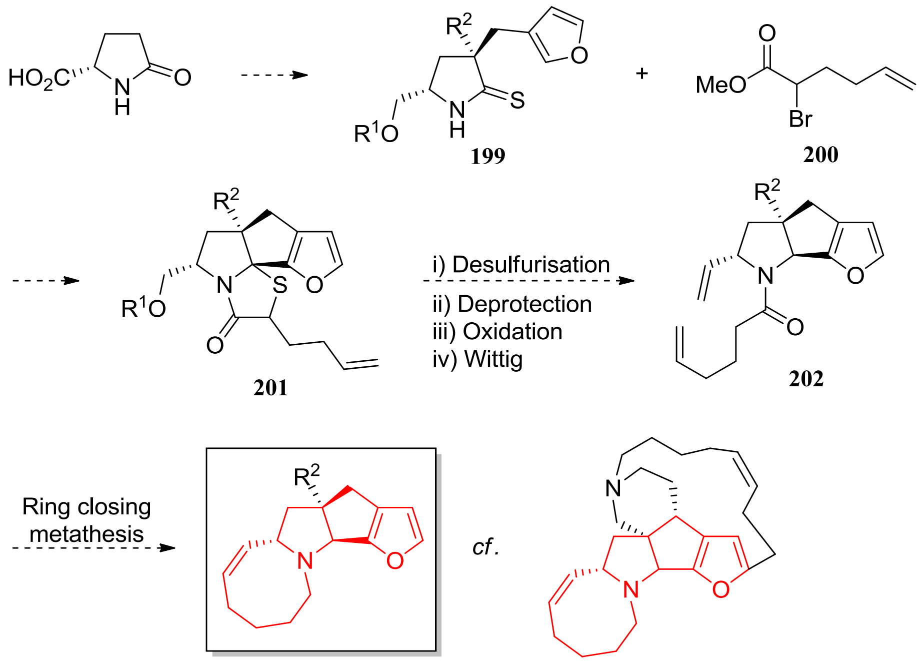
Table 3: Attempts at a thio *N*-acyliminium ion/furan cyclisation of thiolactam **198**.

2.2. Synthesis of the BCDE ring system of ent-(+)-nakadomarin A

2.2.1. Application of the furan-iminium ion methodology

With an optimised procedure for cyclising a furan ring onto an iminium ion in hand, our attention turned to applying this protocol to the synthesis of the core of nakadomarin. The plan was to begin with pyroglutamic acid and convert it to a suitable thiolactam, which would be followed by cyclisation with an appropriate α-bromoester. The synthesis of the naturally occurring enantiomer requires the use of (*R*)-pyroglutamic acid, however the relatively inexpensive (*S*)-pyroglutamic acid was used for these initial studies.

After the synthesis of a thiolactam with the general structure of **199**, a cyclisation would be carried out with α-bromoester **200**, thus forming tetracycle **201** and installing a side chain which could be used to synthesise the 8-membered E ring. Desulfurisation of **201** would be followed by deprotection to give a free hydroxyl group. This would be oxidised to an aldehyde followed by a Wittig reaction to give diene **202**. Finally, a ring closing metathesis of diene **202** would form the 8-membered E ring, thereby completing the construction of the BCDE ring system (Scheme 69).

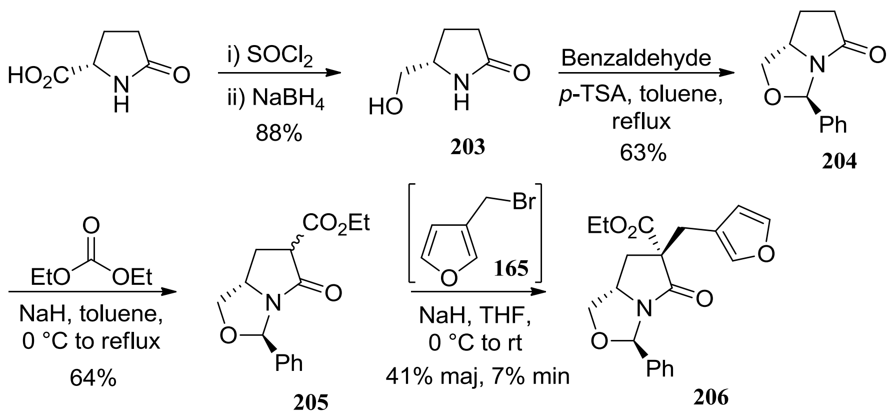


Scheme 69: Application of the thio *N*-acyliminium ion/furan cyclisation strategy to the BCDE ring system.

2.2.2. Synthesis of the cyclisation precursor and α-bromoester

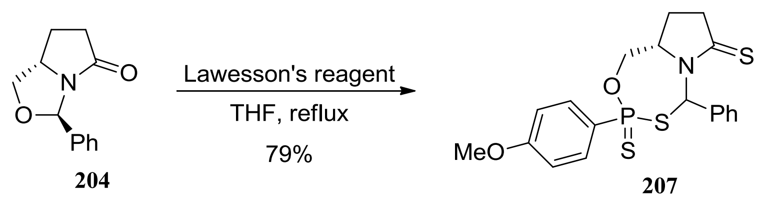
The synthesis of the BCDE ring system began with procedures outlined by Moloney,[82] who had shown that functionalised pyrrolidinones can be synthesised from pyroglutamic acid. Preparation of the cyclisation precursor started with the reduction of (*S*)-pyroglutamic acid (Scheme 70). This was achieved through a conversion of the carboxylic acid to an acyl chloride with $SOCl_2$, followed by reaction with MeOH to give a methyl ester. Subsequent reduction of the methyl ester with $NaBH_4$ gave pyroglutaminol **203**.[83] Condensation of pyroglutaminol **203** with benzaldehyde gave benzylidene *N*,*O*-acetal **204**, thus protecting the amide and alcohol functionalities in 1 step.[84] Additionally, the stereodefined benzylidene ring could impart facial selectivity in the subsequent alkylation step, favouring the formation of the desired *exo*-isomer.

Acylation of benzylidene *N*,*O*-acetal **204** was carried out using NaH to deprotonate the lactam followed by reaction with diethyl carbonate, which gave α-acylated bicycle **205** as an inconsequential 13:1 mixture of diastereoisomers. This was deprotonated with NaH and subsequently alkylated with a solution of bromide **165** in THF, which gave **206** as a 5:1 mixture of diastereoisomers. The major diastereoisomer, presumed to be **206** by analogy with Moloney's work, was isolated in 41% yield. The diastereoselectivity is similar to that obtained by Moloney (7:1) in an alkylation of **205** with benzyl bromide.



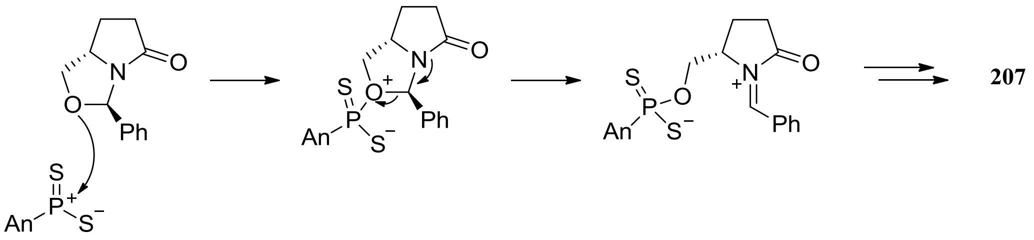
Scheme 70: Synthesis of bicyclic lactam **206**.

The thionation of lactam **206** was attempted with Lawesson's reagent in THF at reflux, which unfortunately gave a complex product mixture. To improve our understanding of this result, the thionation was repeated on a simple bicyclic lactam, which allowed for the isolation of a single major product (Scheme 71). Large coupling constants in the ^{1}H NMR spectrum (*ca*. 28 Hz) suggested our product contained phosphorus and upon closer inspection of the 2D spectra we deduced the identity of the product as oxathiaphosphepane **207**.



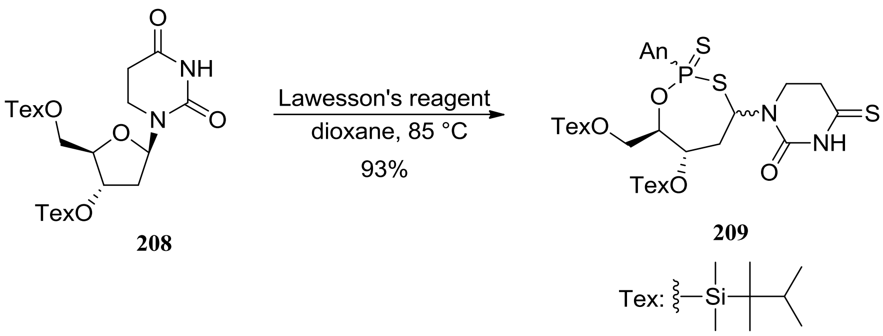
Scheme 71: Attempt at the thionation of **204** led to the incorporation of Lawesson's reagent within the benzylidene *N,O* acetal group.

The reaction of the lactam oxygen with a dithiophosphine ylide, which is in equilibrium with the Lawesson's reagent, converts the substrate to the thiolactam. However, the nucleophilic oxygen atom contained in the oxazolidine ring can also react with the dithiophosphine ylide giving the unwanted integration of the thionating agent (Scheme 72).



Scheme 72: Proposed mechanism of the formation of oxathiaphosphepane **207**.

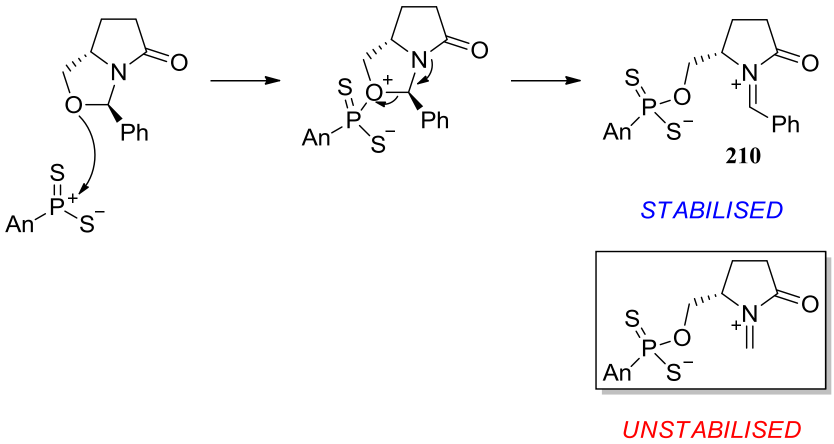
Precedent for a similar type of reaction was scarce; a literature search revealed one example from the work of Clivio, who attempted a thionation of uridine **208**, and instead isolated oxathiaphosphepane **209** as a mixture of diastereoisomers (Scheme 73).[85]



Scheme 73: Literature precedent for the reaction shown in Scheme 71 taken from the work of Clivio.

Clivio found that upon heating oxathiaphosphepane **209** in pyridine, a thermal rearrangement occurred, which afforded the desired thiouridine. Unfortunately, application of these conditions to **207** led to a recovery of starting material.

It was believed that the ease of the oxazolidine ring opening could be dependent upon how well the resultant iminium ion was stabilised. As the iminium ion in **210** is conjugated with the phenyl ring, a fragmentation of the oxazolidine ring is favoured. Replacing the phenyl ring with a group that is less able to stabilise the iminium ion should make the oxazolidine ring less likely to open (Scheme 74).

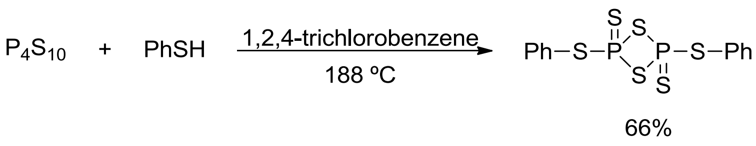


Scheme 74: A comparison of a stabilised and unstabilised iminium ion following the reaction of an oxazolidine ring with Lawesson's reagent.

It was decided that to avoid the formation of oxathiaphosphepane by-products an isopropylidene protection would be attempted.[86] The isopropylidene *N*,*O*-acetal would have an advantage over **204** as there would be increased steric hindrance on the *endo*-face of the bicyclic system, which could potentially improve the stereoselectivity of the thio-Claisen rearrangement. The protection was carried out in toluene and gave fused oxazolidine **211** (Scheme 76).

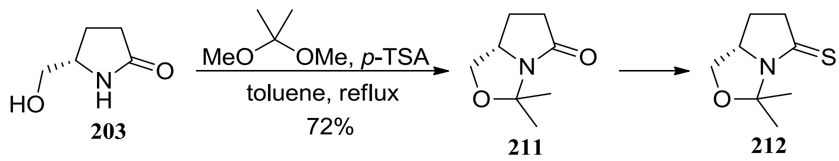
To see if using **211** was a viable alternative to the benzylidene, a thionation of the unsubstituted bicyclic lactam was attempted, first with Lawesson's reagent in THF (Table 4, entry 1). Although some decomposition was observed, a small amount of what was tentatively assigned as thiolactam **212** could also be seen in the reaction mixture. Changing from THF to toluene improved the ratio to 2:1 in favour of the starting material (entry 2). Additionally, less decomposition was observed in the ^{1}H NMR spectrum. An increase in temperature to 65 ^{o}C allowed for the isolation of **212** in a modest yield. This rose to 31% following an increase in temperature to 75 ^{o}C.

Yokoyama *et al*. developed a novel thionating agent, which allowed the rapid conversion of amides to thioamides in THF at ambient temperature.[87] Yokoyama's reagent was synthesised from phosphorus pentasulfide and thiophenol (Scheme 75).



Scheme 75: Synthesis of Yokoyama's reagent.

Efforts at thionating **211** using Yokoyama's reagent in various solvents led to a decomposition of the starting material. No reaction was observed when a P_4S_{10}-pyridine complex was used,[88] however when the thionation was attempted with P_4S_{10}, a 1:1 mixture of lactam and thiolactam was observed. The reaction was very clean in comparison to previous attempts, with very little other than product and starting material observed in the crude ^{1}H NMR spectrum. Unfortunately, thiolactam **212** was isolated in a very poor yield of 6%.

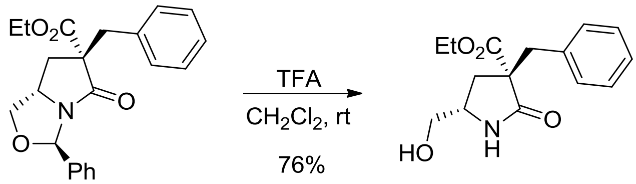


Scheme 76

Entry	Conditions	Yield of **212**/Ratio of **211**:**212**
1	Lawesson's reagent (0.5 eq), THF, 55 ^oC, 20 h	3:1[a]
2	Lawesson's reagent (0.5 eq), toluene, 55 ^oC, 19 h	2:1[a]
3	Lawesson's reagent (0.5 eq), toluene, 65 ^oC, 19 h	27%
4	Lawesson's reagent (0.5 eq), toluene, 75 ^oC, 19 h	31%
5	Yokoyama's reagent (0.6 eq), THF, rt, 30 mins	0[b]
6	Yokoyama's reagent (0.55 eq), toluene, rt, overnight	0[b]
7	Yokoyama's reagent (0.55 eq), CH_2Cl_2, rt, 3 h	0[b]
8	P_4S_{10}-pyridine (0.3 eq), MeCN, rt, 4 h	0[c]
9	P_4S_{10} (1 eq), toluene, reflux, 2 h	1:1[a,d]
[a] Ratio determined by ^{1}H NMR analysis, [b] decomposition, [c] starting material observed, [d] no change in ratio beyond 2 h, clean crude reaction mixture by ^{1}H NMR analysis, very low yield of product, 6%.		

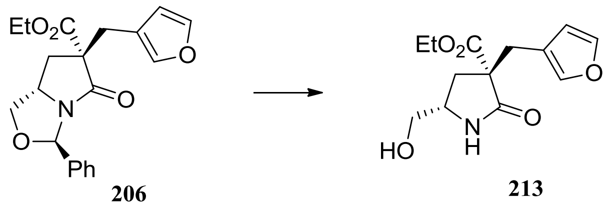
Table 4: Attempted thionation of isopropylidene *N,O*-acetal **211** with a variety of thionating agents and conditions.

Following the unsatisfactory results obtained from thionating lactam **211**, a change was made to the synthetic route. A thionation of a secondary lactam was considered, which required the removal of the benzylidene protecting group in lactam **206**. Moloney was able to carry out an acid mediated removal of a benzylidene group through the use of TFA (Scheme 77).[82]



Scheme 77: Acid mediated removal of the benzylidene *N*,*O*-acetal.

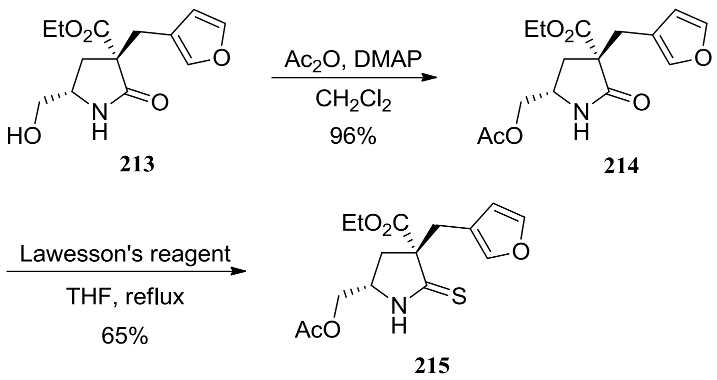
However, when these conditions were applied to our substrate a complex mixture was obtained (Table 5, entry 1). The use of strongly acidic conditions could have promoted side reactions involving the labile furan ring, leading to decomposition. The deprotection was repeated under milder conditions using *p*-TSA, which gave alcohol **213** in a modest yield of 39% (entry 2). Carrying out the deprotection in $CHCl_3$ and refluxing conditions led to decomposition (entry 3). A change of solvent to THF gave a 1:1 mixture of benzylidene *N*,*O*-acetal and alcohol (entry 4). The most promising result was obtained when the deprotection was carried out with *p*-TSA in CH_2Cl_2 followed by immediate purification of the reaction solution by flash chromatography, which gave alcohol **213** in an 87% yield (entry 5).



Entry	Conditions	Yield%
1	TFA (10 eq), CH_2Cl_2, rt, 3.5 h	0[a]
2	*p*-TSA (1eq), $CHCl_3$, rt, 16 h	39%
3	*p*-TSA (1 eq), $CHCl_3$, reflux, 18 h	0[a]
4	*p*-TSA (0.1 eq), H_2O (1 eq), THF, rt, 24 h	1:1[b]
5	*p*-TSA (1 eq), CH_2Cl_2, rt, 1.5 h	87%
[a] Decomposition [b] ^{1}H NMR analysis showed a 1:1 ratio of starting material to product.		

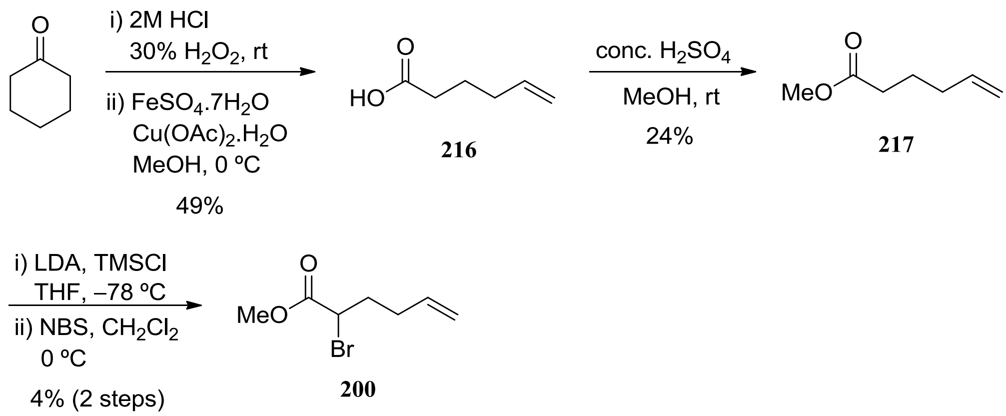
Table 5: Attempts at the removal of the benzylidene protecting group using TFA and *p*-TSA.

Attention was next turned to the protection of the alcohol group in lactam **213**. Protection by acetylation was chosen as it allowed for the selective protection of the alcohol in the presence of the amide. This was accomplished using Ac_2O, which gave acetate **214** (Scheme 78). Subsequent thionation with Lawesson's reagent gave thiolactam **215** in a 65% yield.



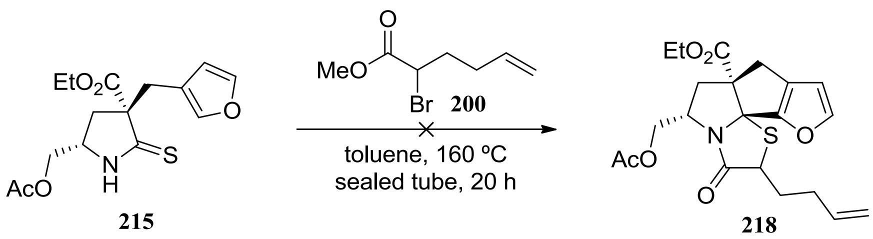
Scheme 78: Synthesis of thiolactam **215**.

With the synthesis of a suitable cyclisation precursor, the next task involved the construction of α-bromoester **200**. This began with the oxidative ring opening of cyclohexanone to give carboxylic acid **216**, containing the key 5-carbon side chain with a terminal alkene (Scheme 79).[89] Cyclohexanone was first converted to a hydroxy peroxide using H_2O_2. This was followed by oxidative radical ring opening with $FeSO_4$ and $Cu(OAc)_2$, which gave carboxylic acid **216**. Subsequent Fisher esterification was carried out in MeOH with a catalytic amount of conc. H_2SO_4 to give methyl ester **217**.[90] The α-bromination was achieved by converting methyl ester **217** to a silyl enol ether by deprotonation with LDA to give an enolate, which was then silylated with TMSCl.[91] Subsequent bromination with NBS gave α-bromoester **200** in a very poor yield.[92]



Scheme 79: Synthesis of α-bromoester **200**.

With α-bromoester **200** in hand, the furan-iminium ion cyclisation of thiolactam **215** was attempted. Unfortunately, the cyclisation to give tetracycle **218** was unsuccessful and the starting thiolactam was recovered (Scheme 80).

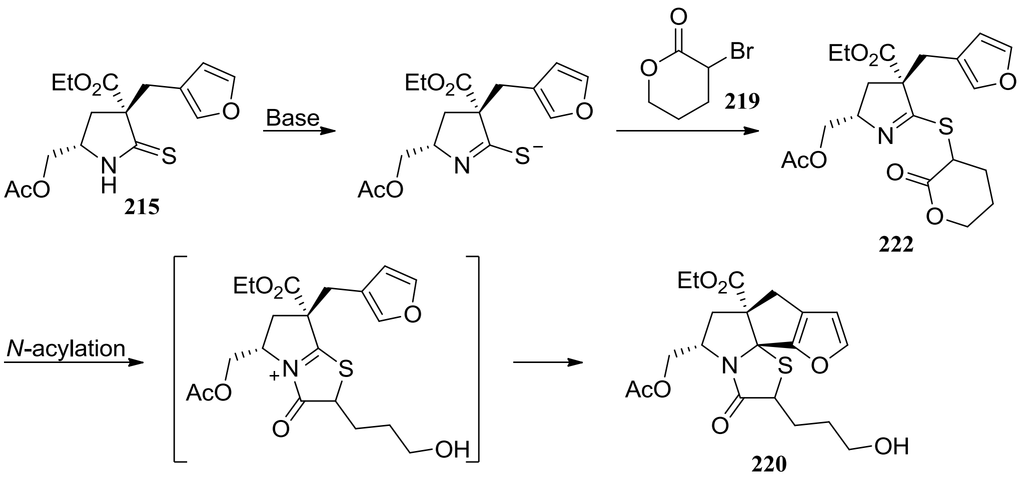


Scheme 80: Attempted thio *N*-acyliminium ion/furan cyclisation of **215** using α-bromoester **200**.

It was thought that *S*-alkylation with a secondary alkyl bromide, and potentially the increased steric hindrance around the nitrogen centre, reduced the rate of reaction relative to the cyclisation carried out on model system **198**.

To increase the probability of forming the thio *N*-acyliminium ion, the reaction protocol was modified to increase the nucleophilicity of the thiolactam. To achieve this, *S*-

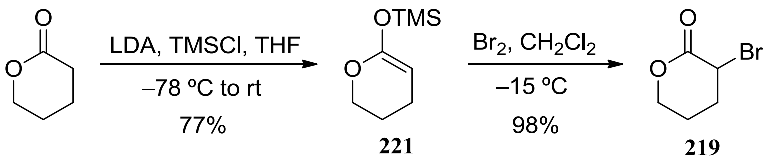
alkylation of thiolactam **215** would be carried out by deprotonating thiolactam **215** first to form a thio-enolate, followed by alkylation with an α-bromoester and isolation of the resultant thioimidate. Subsequent intramolecular *N*-acylation of the resultant thioimidate would be carried out separately. A further modification to the strategy was the change of α-bromoester **200** to α-bromo lactone **219**, as the synthesis of the lactone should be concise relative to **200**. Ring opening of the lactone moiety during *N*-acylation and furan cyclisation would give tetracycle **220**. The side chain formed following lactone ring opening would be used to construct the E ring (Scheme 81).



Scheme 81: Modified strategy involving a deprotonation of **215** to give a more reactive thio enolate which will be alkylated with the more accessible lactone **219**.

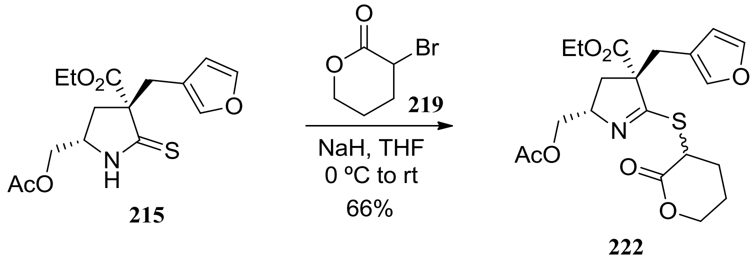
Work on this modified protocol began with the synthesis of lactone **219**. The first attempt involved heating a mixture of δ-valerolactone with PBr_3 in Br_2, which ultimately led to decomposition.[93] The next attempt consisted of a deprotonation of the lactone with LDA followed by an attempted bromination with NBS, which was also unsuccessful with recovery of the starting lactone,.[94]

The synthesis of α-bromoester **200** *via* a silyl enol ether had been successful, although the product was isolated in a very low yield. The same procedure was followed in the synthesis of **219**, by converting δ-valerolactone to silyl enol ether **221** using LDA and TMSCl (Scheme 82).[91] In the synthesis of **200**, the crude silyl enol ether was subjected to the bromination. The low yield obtained could have been attributed to the lack of a purification step, therefore silyl enol ether **221** was purified by distillation, affording the product in 77% yield; bromination then gave bromide **219** in near quantitative yield.[95]



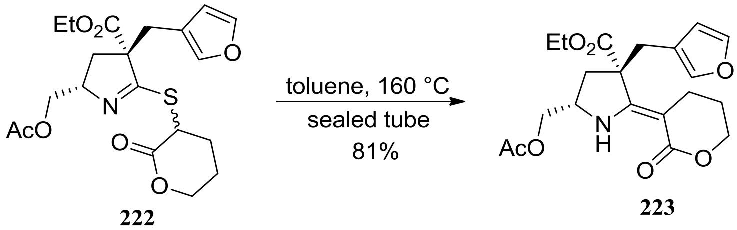
Scheme 82: Synthesis of α-bromolactone **219** from δ-valerolactone *via* silyl enol ether **221.**

Next our attention turned to the synthesis of thioimidate **222**. This was achieved by deprotonating thiolactam **215** with NaH to give a thioenolate followed by alkylation with bromide **219**, which gave **222** as an inseparable mixture of diastereoisomers (Scheme 83).



Scheme 83: Deprotonation of thiolactam **215** followed by *S*-alkylation vith **219** to give thioimidate **222**.

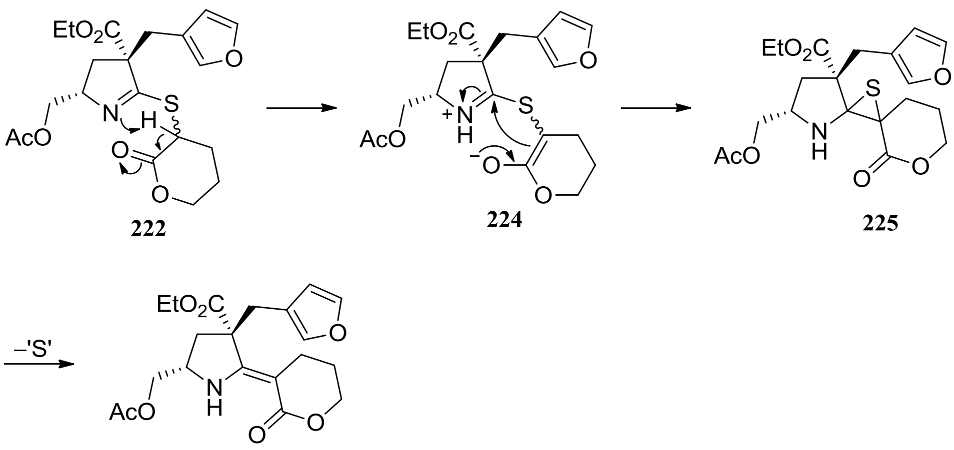
The furan-iminium ion cyclisation of thioimidate **222** was carried out by heating in toluene at 160 °C in a sealed tube. Unfortunately, thioimidate **222** had converted cleanly to an unknown single product. The lack of diastereoisomers suggested the α-carbon atom of the lactone had participated in the reaction and after careful analysis of the ^{1}H NMR spectra we identified the product as amine **223** (Scheme 84).



Scheme 84: Attempted thio *N*-acyliminium ion/furan cyclisation of **222** led to the formation of vinylogous carbamate **223**.

Compound **223** appears to be the product of an Eschenmoser sulfide contraction.[96] Typical conditions for such reactions, however, require both a base and a thiophile such as a phosphite (Scheme 85), but neither was present in the reaction of thioimidate **222**.

One possibility is that the imine acts as a base to remove the lactone α-proton to give **224**, containing an iminium ion and an enolate moiety. Nucleophilic attack of the enolate functionality onto the electrophilic carbon atom of the iminium ion could have formed episulfide **225**, followed by a desulfurisation to give the observed product. However, the mechanism of desulfurisation in the absence of a thiophile is unclear, although it was presumed the elevated temperature and pressure of the reaction contributed to the loss of the sulfur atom.

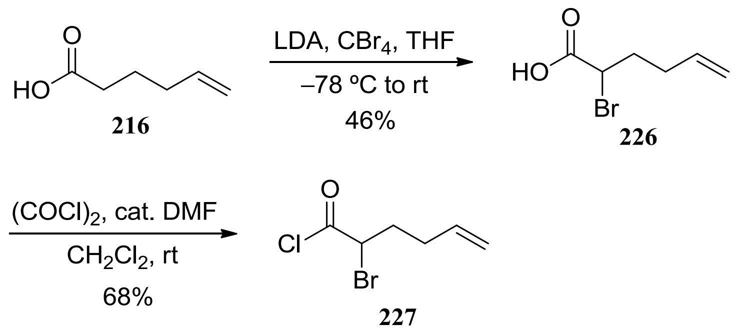


Scheme 85: Proposed mechanism to vinylogous carbamate **223**.

2.2.3. The use of an α-bromo acyl chloride in the cyclisation

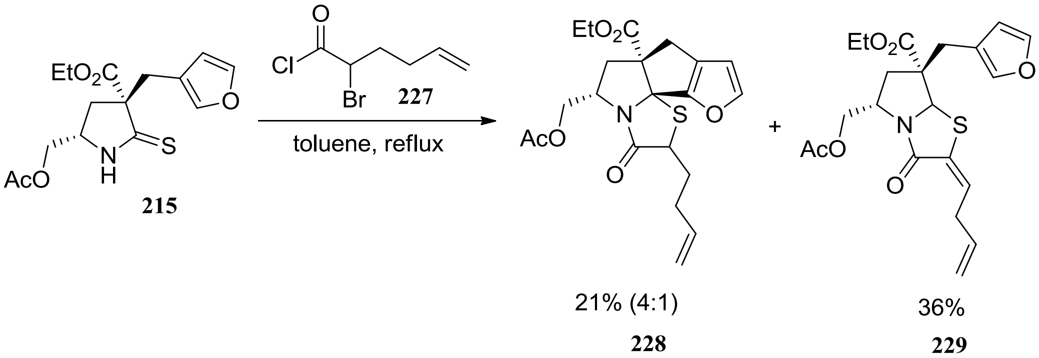
The relatively low reactivity of the ester group could have been the underlying cause of the failure of the cyclisation reactions. With the added steric bulk around the nitrogen atom of thiolactam **215** in comparison to model system **198**, a more reactive alternative to the ester group was needed. As we had experienced some success with acyl chlorides, the next strategy involved the use of an α-bromo acyl chloride similar to that used by Padwa in Scheme 43.[73]

A suitable bromoacetyl chloride was synthesised following conditions outlined by Padwa *et al*. (Scheme 86).[73] The α-bromination of carboxylic acid **216** was achieved with two equivalents of LDA to convert **216** to a lithium carboxylate salt and to carry out an α-deprotonation of the carboxylate group. Bromination with CBr_4 gave compound **226**. Conversion to acyl chloride **227** was accomplished with $(COCl)_2$ and a catalytic amount of DMF.



Scheme 86: Synthesis of acyl chloride **227**.

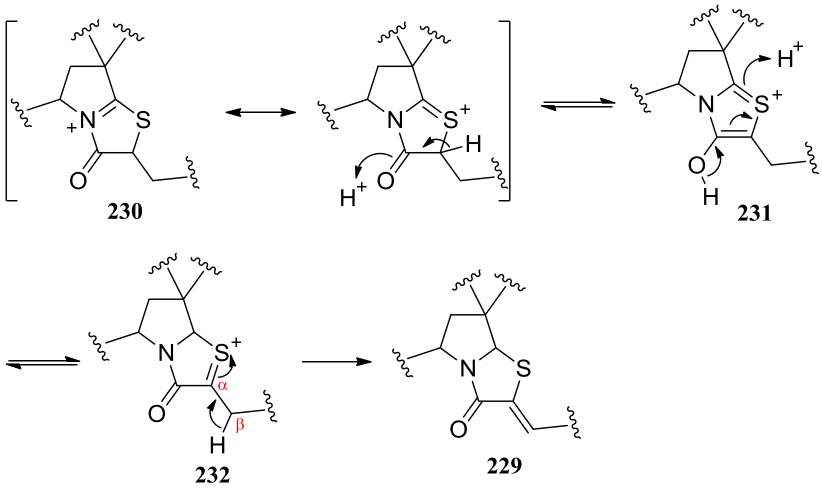
Following the synthesis of **227**, the cyclisation reaction was attempted under analogous conditions to those used previously in the synthesis of tetracycle **191**. The cyclisation of thiolactam **215** with bromide **227** was carried out in toluene under reflux, enabling the successful synthesis of **228** as a mixture of diastereoisomers in a poor yield (Scheme 87).



Scheme 87: The thio *N*-acyliminium ion/furan cyclisation of **215** with acyl chloride **227** led to the formation of the desired product and a significant amount of uncyclised product **229**.

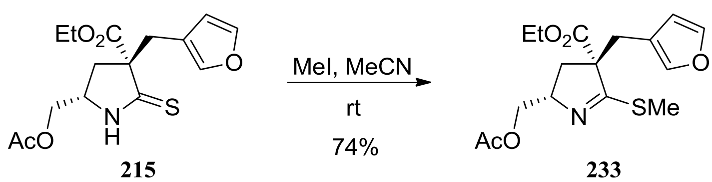
The low yield of the cyclisation was attributed to the formation of a considerable amount of a by-product, along with decomposition. After extensive NMR spectroscopic work, the by-product was identified as **229** as a single unidentified diastereoisomer, along with significant decomposition.

A possible mechanism to **229** is outlined in Scheme 88. The reaction of thiolactam **77** with bromoacetyl chloride **227** gives iminium ion **230**, which is a common intermediate in the mechanistic pathways of both products. A nucleophilic attack from the furan ring gives **228**. Some of this intermediate undergoes keto-enol tautomerism to give **231**, which is driven by the formation of the aromatic thiazolium ring. Tautomerism to the keto form gives **232** followed by loss of the β-hydrogen to give **229**. The product distribution suggests that this pathway seemed to be more favourable than the reaction of the iminium ion with the furan ring.



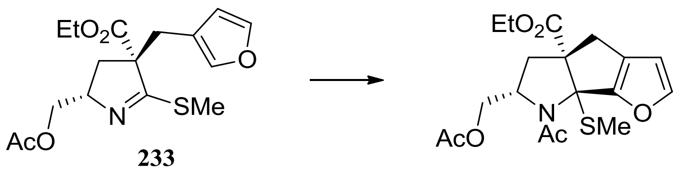
Scheme 88: Proposed mechanism of formation of **229**.

Carrying out the *S*-alkylation and *N*-acylation with two separate reagents could eliminate this mechanistic pathway, thus lowering the acidity of the β-hydrogen and thereby improving the selectivity of the reaction. To achieve this, alkylation of thiolactam **215** would be carried out with an alkyl halide to give a thioimidate. Subsequent *N*-acylation could form an iminium ion, followed by cyclisation from the furan ring. The *S*-alkylation was completed using MeI to give thioimidate **233** (Scheme 89).



Scheme 89: S-methylation of **215** with MeI to give thioimidate **233**.

Attempts at *N*-acylation of thioimidate **233** are summarised below (Table 6). The first attempt with AcCl and NEt_3 was unsuccessful, with the recovery of starting material. The reaction was repeated with a change of base and carried out in various solvents at elevated temperature with similar outcomes. The acylating agent was changed to Ac_2O which was used as solvent, but unfortunately the desired product was not synthesised. It was clear that the intramolecular nature of the acylation in the reaction of **215** was important, and that **233** was insufficiently nucleophilic to react intermolecularly with acylating agents.



Entry	Conditions	Yield%
1	AcCl (1.1 eq), NEt_3, (1.1 eq), CH_2Cl_2, rt 4 h	0[a]
2	AcCl (1.1 eq), DMAP (0.1 eq), CH_2Cl_2, rt, 4 h	0[a]
3	AcCl (1.1 eq), K_2CO_3 (0.1 eq), CH_2Cl_2, rt	0[a]
4	AcCl (1.1 eq), 4 Å molecular sieves, CH_2Cl_2, 5 h, reflux	0[a]
5	AcCl (1.1 eq), MeCN, reflux	0[a]
6	AcCl (1.1 eq), toluene, reflux, 4 h	0[a]
7	Ac_2O (solvent), 100 °C, 4 h	0[a]
8	Ac_2O (solvent), NEt_3 (1.1 eq), 100 °C	0[a]
[a] Starting material obtained, significant peak broadening in ^1H NMR spectrum.		

Table 6: Attempts at *N*-acylation of **233** using AcCl and Ac_2O.

2.3. Synthesis of the ABCD ring system of *ent*-(+)-nakadomarin A *via* a thio-Claisen rearrangement using a *Z*-allylic bromide

So far, the approaches taken in the synthesis of the carbocyclic B ring have all depended on a nucleophilic attack from a furan ring onto an iminium ion, but the relative nucleophilicity of the furan compared to other nucleophiles was unknown. The Padwa group have shown that indoles and methoxyphenyl groups react with thio-*N*-acyliminium ions, however examples of a furan ring participating in this reaction could not be found in the literature.

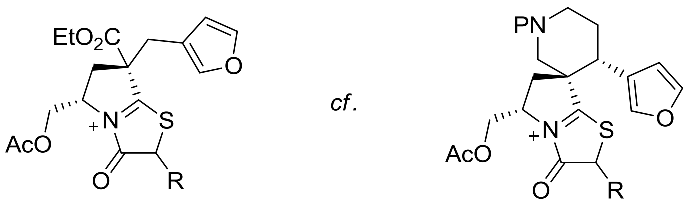
The Mayr group have been able to quantify the relative strength of nucleophiles and electrophiles, and by using this data and the Mayr-Patz equation shown below, can predict absolute rate constants of various reactions (Equation 1).[97, 98] This equation shows the relationship between the rate constant k, nucleophilicity parameter N, electrophilicity parameter E and the nucleophile-specific sensitivity parameter s.

$$\log k = s(N + E)$$

Equation 1: The Mayr-Patz equation.

Using this equation and the reactivity parameters, the relative nucleophilicity of an indole could be compared with that of a furan. After an extensive search of Mayr's database of reactivity parameters, a Vilsmeier iminium ion was chosen for this comparative study as its electrophilicity was the most comparable to that of a thio *N*-acyliminium ion. This electrophile has an electrophilicity parameter E=–5.77;[99] for furan, the nucleophilicity parameter N=1.33 and the sensitivity parameter s=1.29,[100] while for indole, the relevant parameters are N=5.55 and s=1.09.[101] Substituting these values into Equation 1 suggests that indole should react approximately 300,000 times faster, which shows a vast difference in the reactivities of the two nucleophiles and could explain why more of **229** had formed than the desired compound in the synthesis of **228**.

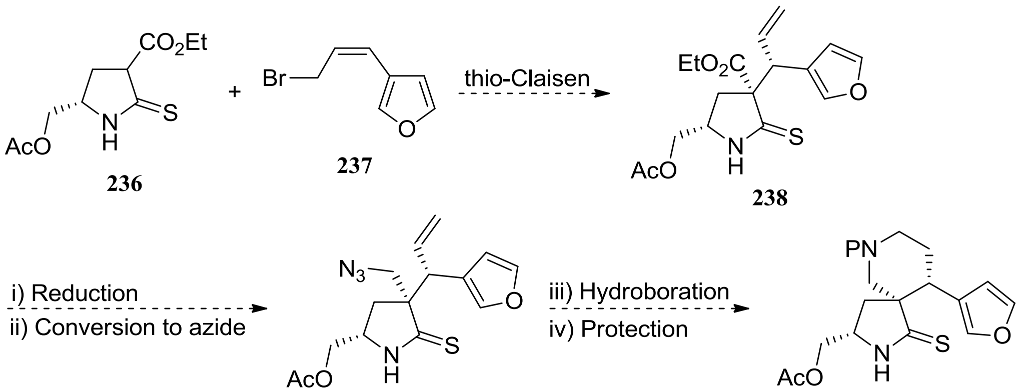
Furan-iminium ion cyclisations have been utilised by a few groups in their syntheses of nakadomarin. The Funk and Zhai syntheses both rely on generating an iminium ion from a Boc-protected pyrrolidine ring which is then attacked by the furan ring. Dixon's first synthesis differs in that the iminium ion does not have an electron withdrawing group on the nitrogen atom, however the furan ring is held in place by the piperidine ring, allowing for the cyclisation of the furan onto a less electrophilic iminium ion. Comparing the thio *N*-acyliminium ion **234** generated from **215** to those generated in the Funk and Zhai syntheses, it is clear that the added electron density from the sulfur substituent reduced its electrophilic character. A possible solution would be to 'fix' the furan in place by synthesising the piperidine ring, thus generating iminium ion **235**. The furan would be in close proximity to the iminium ion, hopefully increasing the rate of the desired cyclisation relative to unwanted pathways and hence improving the selectivity of the reaction (Figure 8).



234 **235**

Figure 8: Comparison of iminium ion **234** with iminium ion **235** which contains the key piperidine ring needed to improve the selectivity of the cyclisation.

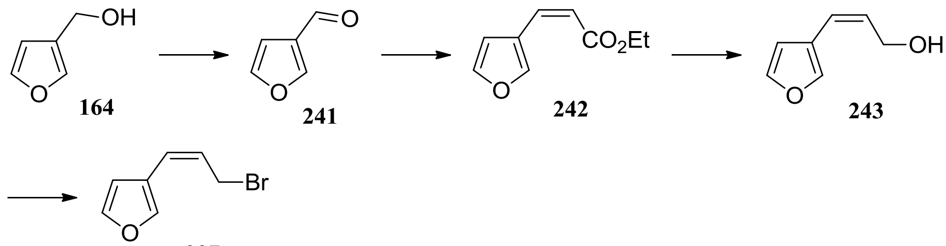
To achieve this, we planned to carry out the thio-Claisen rearrangement with secondary thiolactam **236** and *Z*-allylic bromide **237**. The sigmatropic rearrangement would pass through the favoured transition state as discussed in section 1.4.1., giving the product with the correct stereochemical configuration. The resulting terminal alkene in **238** would be used to synthesise the piperidine ring. This would be accomplished by reducing the ester to an alcohol. Mesylation and subsequent conversion to an azide group would give **239**. Subjecting the azide to the hydroboration-cycloaddition conditions developed by Evans would give the piperidine ring.[29] Subsequent amine protection would give cyclisation precursor **240** (Scheme 90).



Scheme 90: Modified strategy involving a thio-Claisen rearrangement. The vinyl and ester functionalities will be converted to the required piperidine ring.

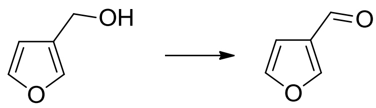
2.3.1. Synthesis of a suitable *Z*-allylic bromide

Work on the ABCD ring system began with the synthesis of allylic bromide **237** for use in the thio-Claisen rearrangement. The plan was to oxidise furan-3-methanol to aldehyde **241** and follow this with a *Z*-selective Horner-Wadsworth-Emmons reaction to give ester **242**. Reduction of the ester would give alcohol **243** and subsequent bromination would give the target bromide (Scheme 91).



Scheme 91: Proposed synthesis of *Z*-allylic bromide **237**, required for the thio-Claisen step.

Efforts towards oxidising alcohol **164** are summarised in Table 7. Use of Parikh-Doering oxidation (entry 1),[102] barium manganate (entry 2)[103] or 2-iodoxybenzoic acid (entry 3)[104] all led to recovery of starting material. The use of Dess-Martin periodinane allowed for the successful synthesis of aldehyde **241**, albeit in a poor yield.[105] Although this method was successful, the large amount of Dess-Martin periodinane needed to convert to the aldehyde due to its high molecular weight was unsatisfactory (entry 4). Swern oxidation was successful, but gave the desired aldehyde in a very low yield (entry 5).[106]



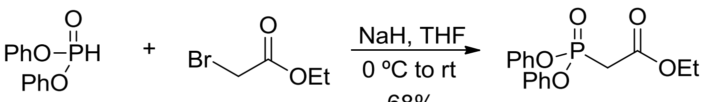
164 **241**

Entry	Conditions	Yield%
1	pyr.SO_3 (1.5 eq), DMSO (2 eq), NEt_3 (6 eq), CH_2Cl_2, 0 °C to rt, 18.5 h	0[a]
2	$BaMnO_4$ (2.5 eq), CH_2Cl_2, rt, 16 h	0[a]
3	IBX (1.1 eq), DMSO, rt, 5 h	0[a]
4	DMP (1.1 eq), H_2O (1.2 eq), CH_2Cl_2, rt, 65 mins	18%
5	$(COCl)_2$ (1.05 eq), DMSO (2.1 eq), NEt_3 (5 eq), –78 °C to rt, 1 h	6%
[a] Starting material obtained.		

Table 7: Attemts at synthesisng aldehyde **241** using various reaction conditions.

Attempts to synthesise aldehyde **241** in a good yield proved ineffective, which led us to believe the product was unstable. Avoiding the isolation of the aldehyde and subjecting the crude product mixture to the next step could solve this problem.

The Horner-Wadsworth-Emmons reaction is a widely used procedure in the synthesis of α,β-unsaturated esters from aldehydes and stabilised phosphonate carbanions. Still and Gennari developed a *Z*-selective modification of this reaction by using trifluoroalkyl esters of the phosphonate group.[107] We chose to adopt the Ando variation of this procedure in the synthesis of **242**, which differs to the Still-Gennari method by replacing the fluoroalkyl groups with relatively inexpensive phenyl rings.[108] The Ando reagent was synthesised by the deprotonation of diphenyl phosphite with NaH followed by alkylation with ethyl bromoacetate, which gave **244** (Scheme 92).[109]

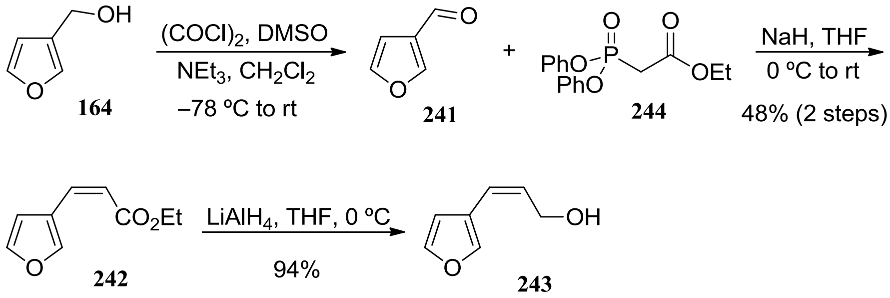


244

Scheme 92: Synthesis of phosphonate **244**.

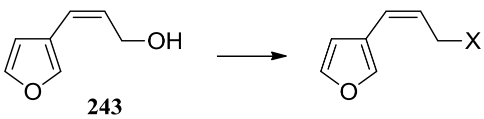
The synthesis of allylic ester **242** began with a Swern oxidation to give aldehyde **241**. The crude product mixture was subjected to a Horner-Wadsworth-Emmons reaction using the

Ando phosphonate, which gave *Z*-allylic ester **242** in a 48% yield over 2 steps. The ester was reduced to alcohol **243** using $LiAlH_4$ in an almost quantitative yield (Scheme 93).



Scheme 93: Synthesis of allylic alcohol **243**.

Attention was next turned to the conversion of allylic alcohol **243** to the corresponding bromide **237**. Analogous conditions to those used to synthesise bromide **165** were employed in the synthesis of **237**, which unfortunately led to a mixture of *Z* and *E* isomers (Table 8, entry 1). Carrying out the reaction at a lower temperature had no effect on the ratio of isomers. To neutralise the acidic by-product, the reaction was with repeated with an excess of CaH_2. Unfortunately, use of base had no effect on the result of the reaction and a mixture of both isomers was obtained. We considered that a more favourable result might be achieved with a change of the bromide to another leaving group. To this end, allylic alcohol **243** was treated with MsCl in an attempt to convert the alcohol group to a mesylate, which also led to a mixture of geometric isomers.

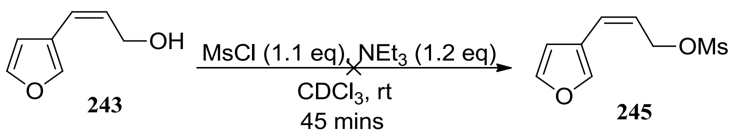


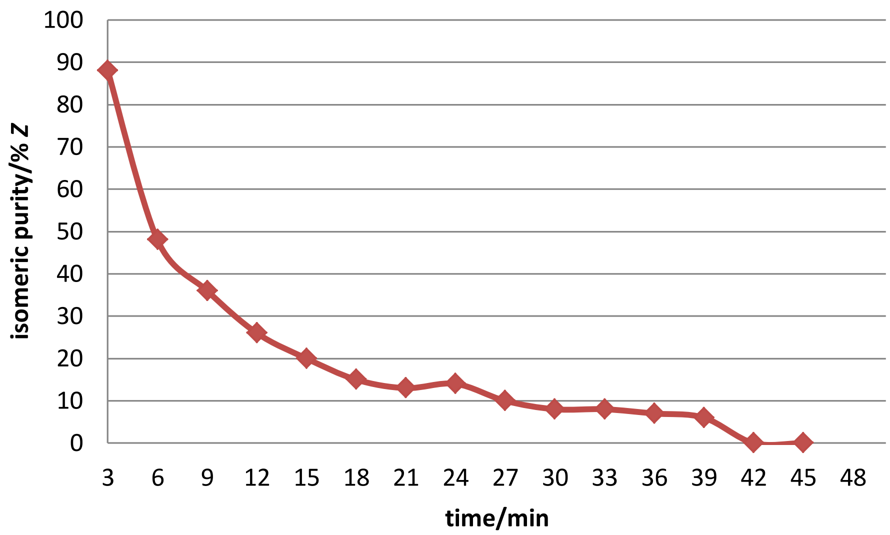
237 X=Br
245 X=OMs

Entry	Conditions	Product	*Z*:*E* ratio
1	PBr_3 (0.4 eq), Et_2O, 0 °C to rt, 30 mins	**237**	1.8:1
2	PBr_3 (0.4 eq), Et_2O, –78 °C to 0 °C, 45 mins	**237**	1.8:1
3	PBr_3 (0.4 eq), CaH_2 (5 eq), Et_2O, –78 °C to 0 °C, 45 mins	**237**	1.3:1
4	MsCl (1.2 eq), NEt_3 (1.4 eq), CH_2Cl_2, 0 °C, 45 mins	**245**	1:1.3

Table 8: Attempts at forming **237** and **245** led to isomeric mixtures.

To determine whether the *E* isomer was forming during the reaction or upon work-up, an NMR experiment was carried out where allylic alcohol **243** was mesylated with MsCl in $CDCl_3$. A total of 15 scans of the reaction were taken at regular 3 minute intervals and the results are displayed in Graph 1. A rapid erosion of stereochemistry was observed, taking place within the first 6 minutes of the reaction. After 3 minutes into the reaction a favourable ratio of *Z* to *E* isomer is observed. As the reaction progresses a steady increase in the amount of the *E* isomer is seen and after 42 minutes the reaction consists exclusively of *E* isomer. It must also be noted that the starting alcohol had been completely consumed within the first three minutes of the reaction.





Graph 1: A graphical representation of the erosion of stereochemistry of the *Z*-allylic mesylate over time.

The results are further illustrated in the ^{1}H NMR spectra below, which show a comparison of the C<u>H</u>$_2$OMs protons of both isomers at 3 minutes and 15 minutes (Figure 9).

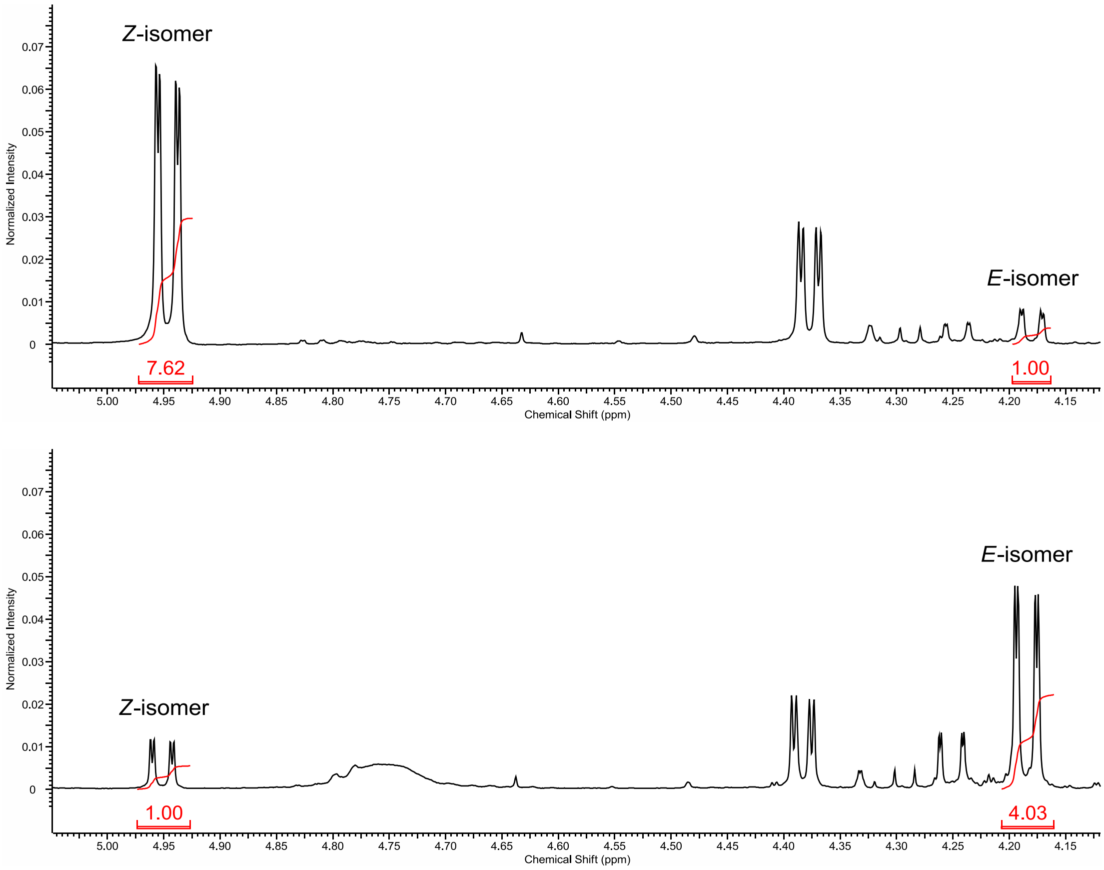
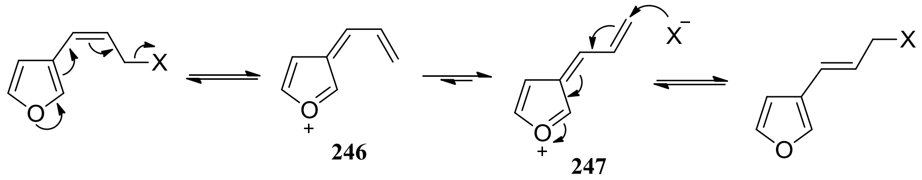


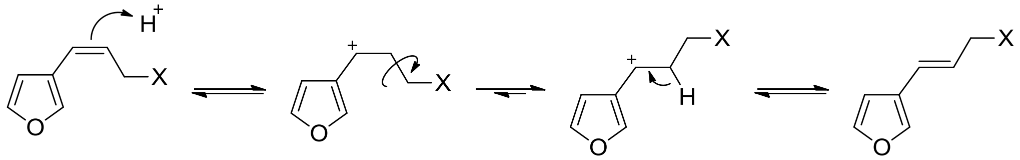
Figure 9: ^{1}H NMR spectra showing a comparison of the $C\underline{H}_2$OMs protons of **245** and the *E*-isomer. The first spectrum was taken at 3 minutes and shows mostly the Z-isomer. The second spectrum was taken 15 minutes into the reaction and shows the E-isomer as the major component of the product mixture.

A key structural feature to both compounds **237** and **245** is the conjugated double bond, which coupled with the furan ring makes this system highly electron-rich. The presence of a good leaving group would make a fragmentation of the molecule favourable. A probable mechanism for this fragmentation is shown in Scheme 94. Loss of the leaving group could form allyl cation **246**, which could interconvert to the more stable rotamer **247**. This could undergo attack from the ejected leaving group and over time more of the thermodynamically favoured *E* isomer would form. This was evidenced by a re-analysis by ^{1}H NMR of the product mixture obtained from entry 1 in Table 8, which showed that after 5 days the product mixture had converted exclusively to the *E* isomer.



Scheme 94: Loss of bromide followed by rotation and nucleophilic of bromide could form the *E*-isomer.

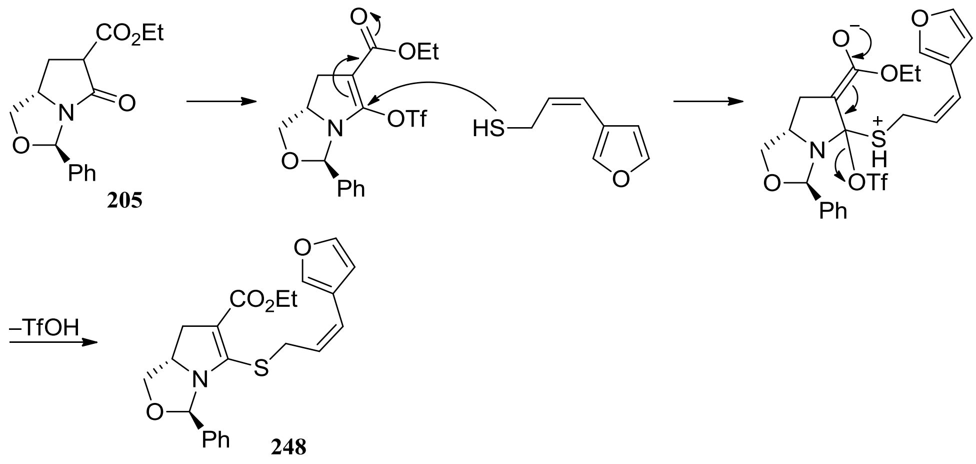
Another explanation for the observed isomerisation involves the protonation of the double bond to give an alkyl cation. Rotation to give the more stable conformer followed by deprotonation could give the *E* isomer (Scheme 95).



Scheme 95: Protonation followed by rotation and loss of a proton could also be probable mechanism in the formation of the *E*-isomer.

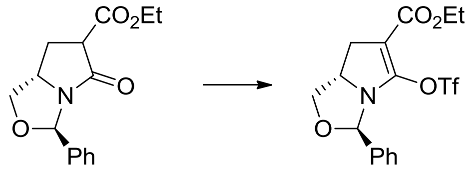
2.3.2. The reaction of a triflate with an allylic sulfide

From the work carried out previously on the attempted syntheses of **237** and **245**, it was clear that a conjugated *cis* double bond was not compatible with a good leaving group in this system. As a *Z*-alkene was needed to give the correct stereochemical configuration following the thio-Claisen rearrangement, a 'role reversal' was considered. Instead of the furan component acting as an electrophile, it would be modified to behave as a nucleophile. As allylic alcohol **243** does not isomerise to the *E* isomer, we would assume, if it could be prepared, the analogous thiol would behave similarly and remain exclusively as the *Z* isomer. This thiol would be expected to react with an electron deficient triflate synthesised from lactam **205**. Subsequent loss of TfOH would give **248** which would undergo the required thio-Claisen rearrangement (Scheme 96).



Scheme 96: Modified strategy involving a triflation of lactam **205**. Nucleophilic attack of the vinyl triflate followed by a loss of the triflate should give the desired cyclisation pre-cursor.

For the first attempt at the triflation, Tf_2NPh was used with NaH to remove the acidic α-proton, which led to the recovery of starting material (Table 9).[110] The reaction was repeated with an increase in the amount of reagents used and carrying it out at an elevated temperature, which also led to no reaction. The last attempt saw the use of Tf_2O, which gave a complex mixture along with the deprotection of the benzylidene group.[111] A search of the literature revealed an unusually low number of triflation reactions of 5-membered lactam rings. It was possible that the additional ring strain experienced in the 5,5-bicyclic ring system may have prevented the triflation from taking place.



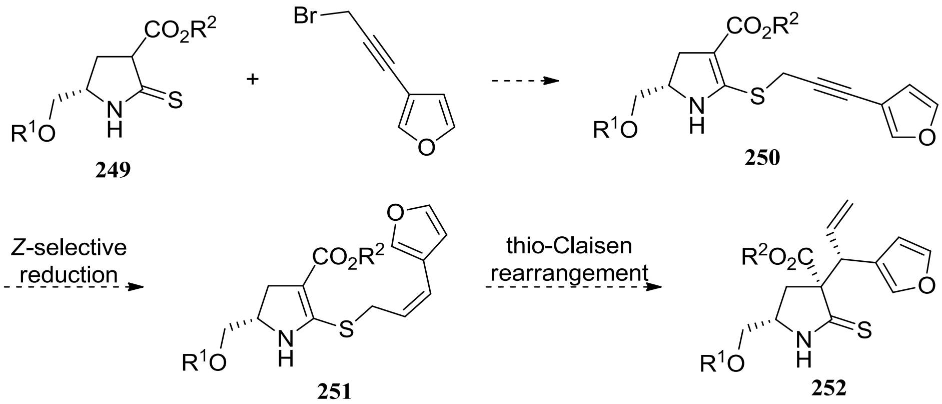
205

Entry	Conditions	Yield
1	Tf_2NPh (1.1 eq), NaH (1.2 eq), THF, 0 °C to rt, 2 h	0[a]
2	Tf_2NPh (1.8 eq), NaH (2.5 eq), THF, 0°C to rt, 2h, then 60 °C for 2 h	0[a]
3	Tf_2O (1.2 eq), NaH (2.5 eq), CH_2Cl_2, –78 °C	0[b]
[a] starting material obtained [b] decomposition, loss of benzylidene protecting group.		

Table 9: Attempts at the triflation of lactam **205**.

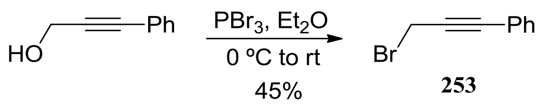
2.3.3. Reduction of an alkyne following *S*-alkylation

Another strategy that would avoid the unstable allylic bromide and mesylate was an *S*-alkylation of a suitable thiolactam with a propargyl bromide, followed by a *Z*-selective reduction (Scheme 97). An unprotected thiolactam with the general structure of **249** should form enamine **250** following *S*-alkylation. Subsequently, the triple bond would be reduced to a Z-alkene, thus giving the rearrangement precursor **251**. Thio-Claisen rearrangement would then give adduct **252**.



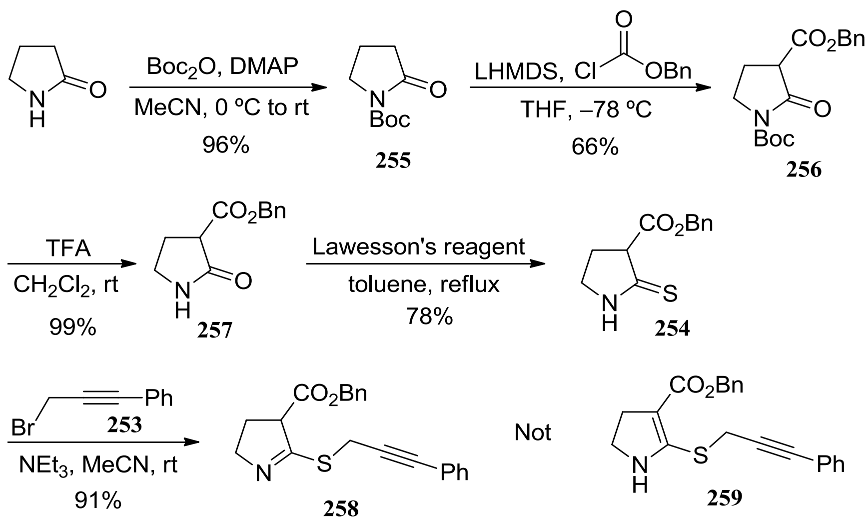
Scheme 97: *Z*-selective reduction following *S*-alkylation.

It was felt that it would be more economical to test the hypothesis on a model system as it would avoid the use of costly chiral material and 3-substituted furan derivatives. A cost effective alternative was to replace the furan with a phenyl ring in the propargyl bromide. The desired bromide was synthesised from phenylpropargyl alcohol using PBr_3 (Scheme 98).[112]



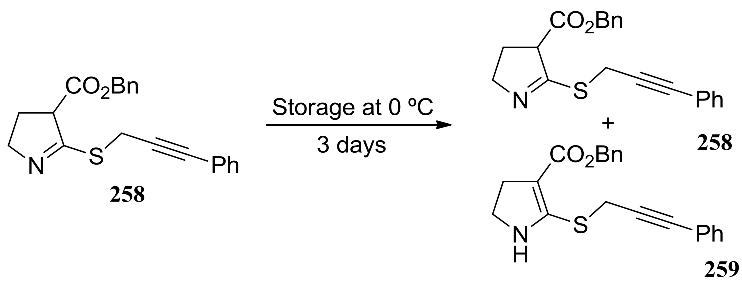
Scheme 98: Synthesis of propargyl bromide **253**.

With the successful synthesis of bromide **253**, work began on the construction of **254** (Scheme 99). Pyrrolidin-2-one was converted to carbamate **255** using Boc_2O.[113] This was deprotonated with LHMDS and acylated with benzyl chloroformate to give **256**.[114] Removal of the Boc group with TFA gave **257**,[115] which was in turn thionated with Lawesson's reagent yielding thiolactam **254**. The unprotected thiolactam was alkylated successfully with bromide **253.** Unfortunately, a thioimidate was synthesised instead of the required enamine. This was surprising as the enamine should be more thermodynamically favourable due to the conjugation of the double bond with the ester group.



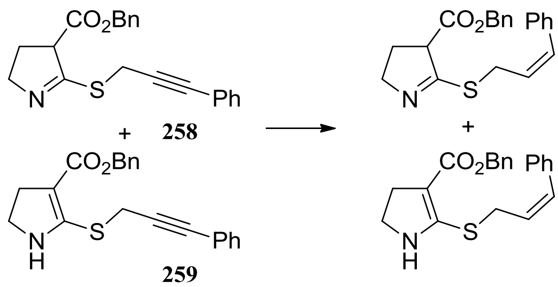
Scheme 99: Attempted synthesis of enamine **258** led to the isolation of imine **258**.

However upon storage at 0 ºC for 3 days, some of the imine isomerised to the enamine giving a 1:1 ratio of **258** to **259** (Scheme 100).



Scheme 100: Upon storage some of imine **258** isomerised to the required enamine.

Nevertheless, the isomeric mixture was submitted to various reduction protocols (Table 10). For the first attempt at reducing alkynes **258** and **259**, Lindlar's catalyst in an atmosphere of H_2 was used, which led to a recovery of starting material.[116] This result was not entirely surprising, as sulfur is known to act as a catalyst poison. The next hydrogenation protocol utilised the *in situ* formation of diimide. This method involves the *syn*-delivery of dihydrogen giving a *cis*-alkene. Generation of diimide was first attempted through the fragmentation of $TsNHNH_2$ with NaOAc, which gave the alkyne starting materials.[117] Increasing the amount of reagent used and carrying out the reaction at a higher temperature also led to a recovery of starting material. For the last effort, the reduction was attempted using *o*-nitrobenzenesulfonyl hydrazide which was formed *in situ*; this reaction was also unsuccessful.[118]



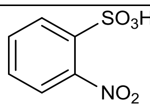
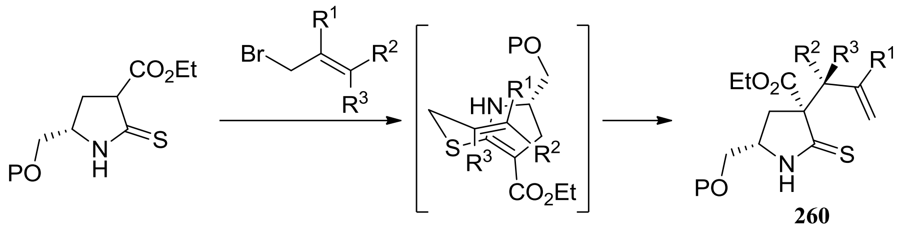
Entry	Conditions	Yield%
1	Lindlar's catalyst (0.05 eq), H_2, EtOH, rt	0[a]
2	$TsNHNH_2$ (2 eq), NaOAc (2.1 eq), THF, reflux, 6 h	0[a]
3	$TsNHNH_2$ (2 eq), NaOAc (3 eq), THF/H_2O (2:1), 100 °C	0[a]
4	 (1 eq), $N_2H_4.H_2O$ (2 eq), MeCN, 0 °C to rt	0[a]
[a] starting material observed.		

Table 10: Attempts at a Z-selective reduction using Lindlar's catalyst and *in situ* generation of diimide.

2.4. Synthesis of the ABCD ring system of *ent*-(+)-nakadomarin A *via* a thio-Claisen rearrangement using an *E*-allylic bromide

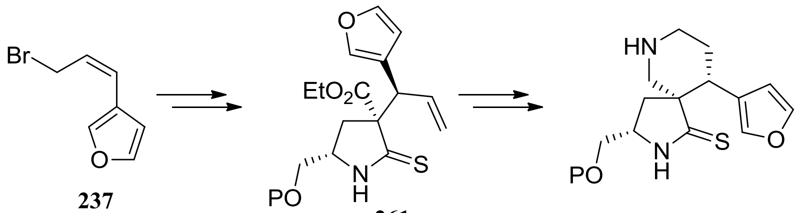
A significant modification to the strategy was needed following the limited success in synthesising suitable precursor compounds for the thio-Claisen rearrangement. The scheme below shows a generic thio-Claisen rearrangement of an unprotected thiolactam with an allylic bromide, which should give compound **260,** arising from the favoured transition state (Scheme 101). This particular scheme illustrates where the substituents on the allylic bromide would be located following the rearrangement, and thus allows for the evaluation of alternative strategies.



260

Scheme 101: Location of substituents on allylic bromide following thio-Claisen rearrangement.

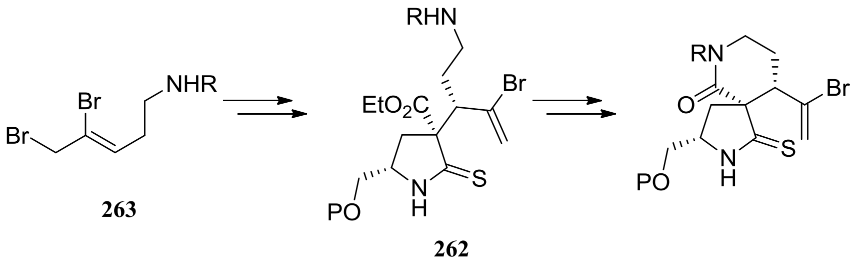
The strategy investigated to date employs a *Z* allylic bromide **237** with R^3 as the furan ring, which following the sigmatropic rearrangement, would give compound **261** with the correct stereochemistry (Scheme 102). The terminal alkene would then be used to construct the piperidine ring through the hydroboration-cycloaddition protocol.



237 **261**

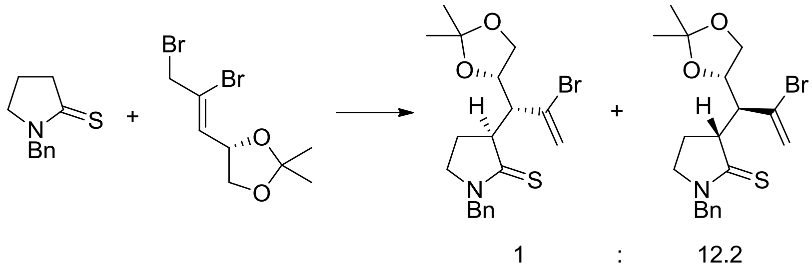
Scheme 102: Existing strategy where the terminal alkene will be used to construct the piperidine ring.

Given the limited stability of compounds such as **237**, another approach would be to use an *E* allylic bromide with R^2 as a precursor to the piperidine ring and R^1 as a functional handle to allow subsequent construction of a furan ring, which would bypass the previous issues with forming isomeric mixtures. Referring back to Scheme 101, it can be seen that using an *E*-allylic bromide would mean the furan ring would have to be synthesised from the terminal alkene. In order to synthesise the piperidine ring, an allylic bromide with an amine functionality would be needed (Scheme 103). As shown below, the thio-Claisen rearrangement would give **262**, with the protected amine group in the correct stereochemical configuration, which should cyclise readily with the ester to form the 6-membered lactam followed by subsequent reduction to a piperidine ring.



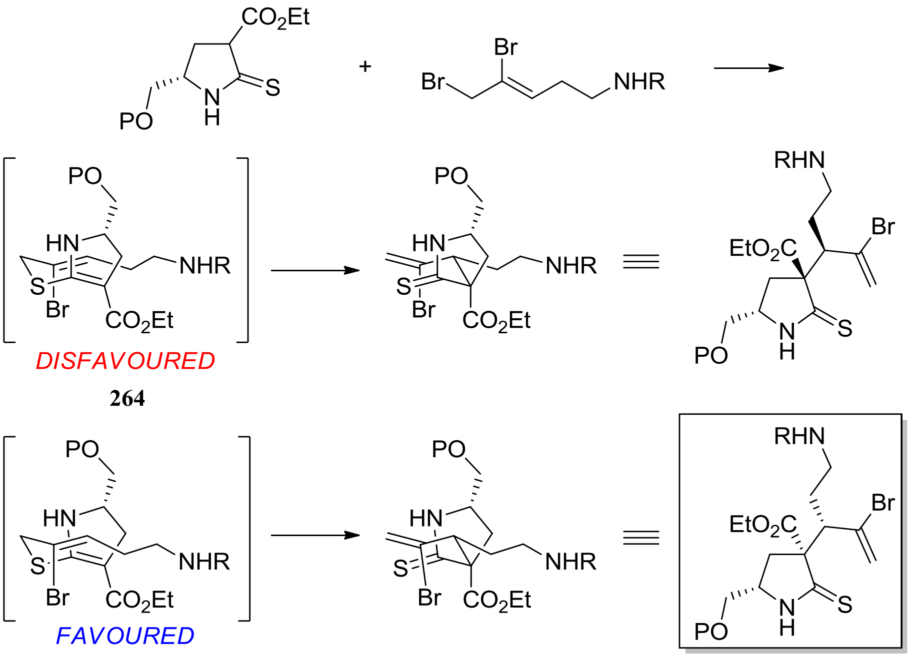
Scheme 103: Modified strategy where the terminal alkene will be used to construct the furan ring.

Previous work in the group has shown that dibromides similar to **263** participate in the thio-Claisen rearrangement. This work has led to an efficient and highly stereoselective preparation of functionalised pyrrolidinethiones (Scheme 104).[119]



Scheme 104: Previous work on the thio-Claisen rearrangement showing the use of a dibromide similar to **263**.

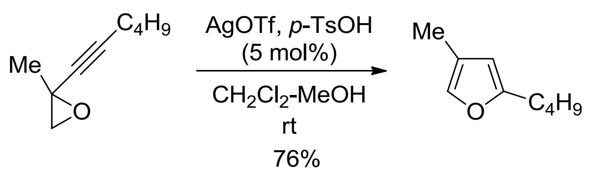
A more detailed explanation of the expected stereochemical outcome of this reaction is shown in Scheme 105. As the thio-Claisen rearrangement can proceed through either a chair or boat like transition state, a total of four diastereoisomers could be formed (although the chair-like transition state is strongly favoured). The two possible chair transition states shown would give the correct relative stereochemistry between the two new stereogenic centres. The existing chiral centre should favour chair transition state **264** over **265**, giving diastereomer **266** as the major product.



264 **265** **266**

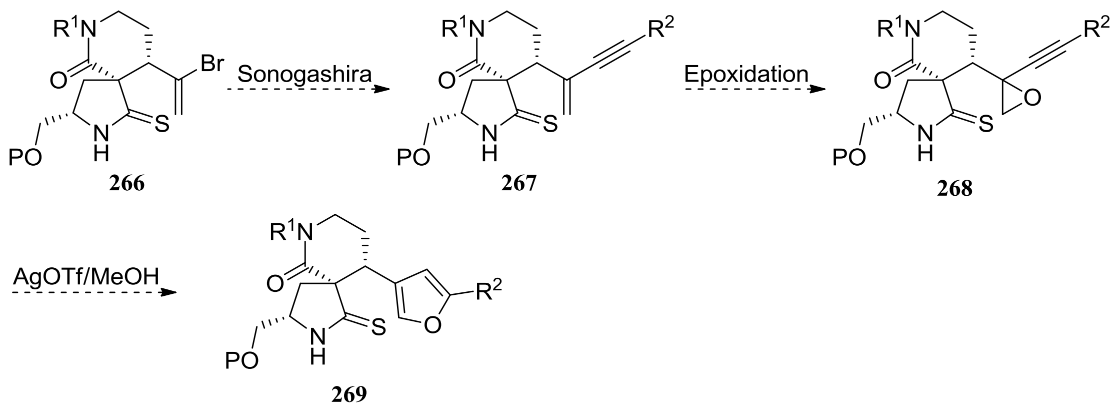
Scheme 105: Comparison of transition states. The stereodefined group should favour transition state **265** which would give the desired diastereoisomer.

Of the various methods of synthesising furan rings, the protocol developed by Pale *et al.* is best suited to vinyl bromide **266**.[120] In their studies, functionalised furans could be formed by a silver(I) catalysed reaction with alkynyl oxiranes in the presence of MeOH (Scheme 106). It is presumed that the first step of the mechanism involves the acid-catalysed opening of the epoxide with MeOH. Cyclisation upon coordination of the alkyne with a silver ion followed by elimination of MeOH gives the furan ring.



Scheme 106: Pale's furan synthesis.[120]

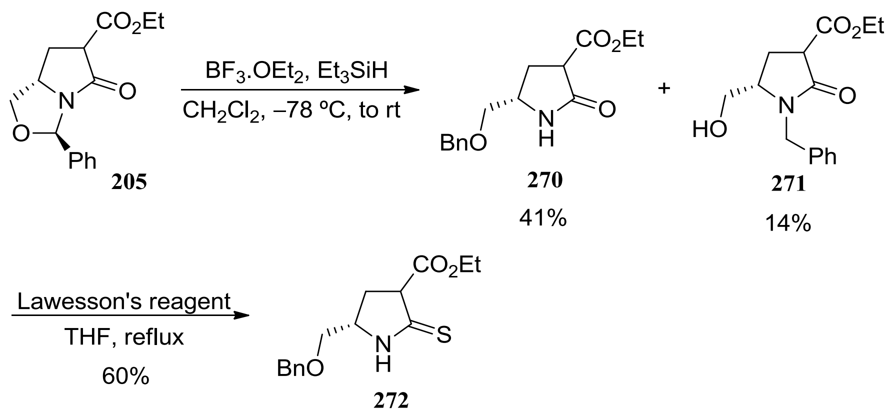
To convert vinyl bromide **266** to an alkynyl oxirane, a Sonogashira coupling will be carried out to give enyne **267**.[121] This could undergo an epoxidation, furnishing alkynyl oxirane **268** ready for conversion to a furan ring which would give cyclisation precursor **269** (Scheme 107).



Scheme 107: Conversion of the vinyl bromide moiety to a furan ring.

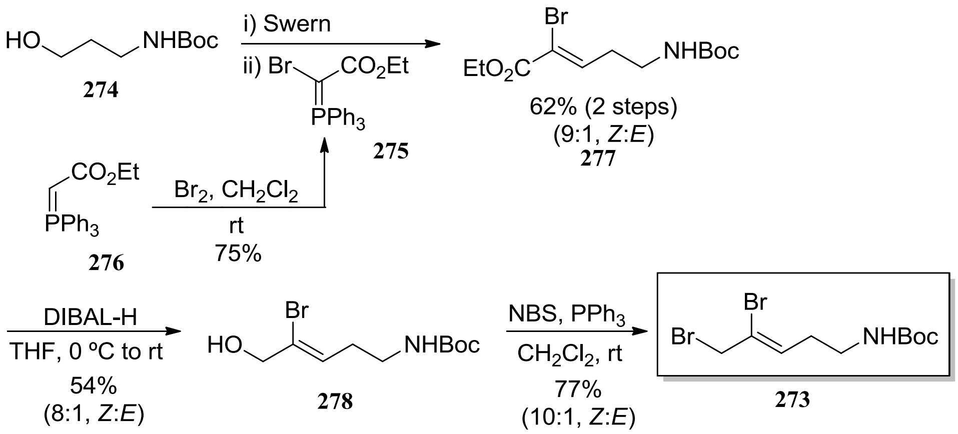
2.4.1. Synthesis of the required thiolactam and *E* allylic bromide

Work on this newly formulated strategy began with synthesis of the compounds required for the thio-Claisen rearrangement, starting with the thiolactam (Scheme 108). Bicyclic lactam **205**, which had been synthesised previously, underwent a reductive oxazolidine ring-opening with BF_3OEt_2 and triethylsilane to give benzyl ether **270**.[122] Along with **270**, *N*-benzylated by-product **271** was also isolated, which was attributed to the Lewis acid coordinating to the oxygen atom within the oxazolidine ring. Thionation of **270** using Lawesson's reagent furnished desired thiolactam **272**.



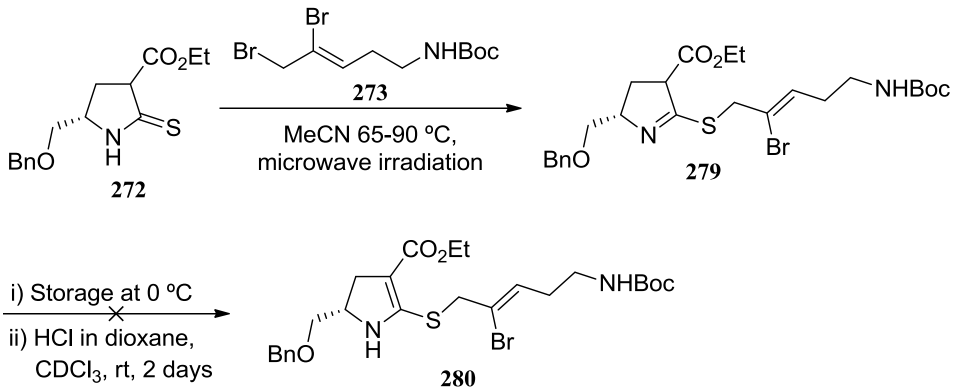
Scheme 108: Reductive ring opening followed by thionation to give thiolactam **272**.

Synthesis of allylic bromide **273** began with a Swern oxidation of alcohol **274**. The inability to isolate the aldehyde following purification meant the crude product mixture was submitted directly to the next reaction. A Wittig reaction of the aldehyde with bromophosphorane **275**, which was synthesised from **276** using Br_2,[123] yielded ester **277** as an inseparable mixture of the *Z* and *E* isomers (9:1). An excess of DIBAL-H was used to reduce the ester and gave allylic alcohol **278** (8:1, *Z*:*E*). Reaction of **278** with NBS/PPh_3 gave the required allylic bromide (10:1, *Z*:*E*) (Scheme 109).



Scheme 109: Synthesis of allylic bromide **273**.

The alkylation of thiolactam **272** with allylic bromide **273** was successful, giving the expected thioimidate **279**. However, after ten days of storage at 0 °C thioimidate **279** had not isomerised to enamine **280**. In an attempt to isomerise to the enamine, **279** was subjected to acidic conditions. Unfortunately, this led to decomposition of the product. Mass spectrometry also indicated the presence of a significant amount of a product with 16 extra mass units. It was presumed that the sulfide could have undergone oxidation to the sulfoxide due to peroxides present in the dioxane (Scheme 110).

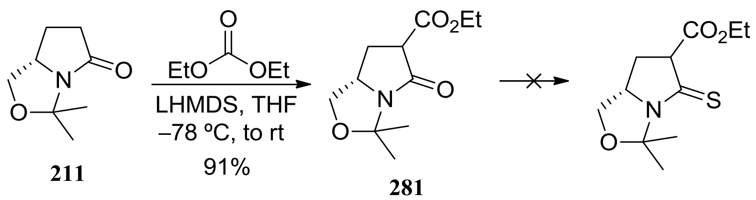


Scheme 110: Attempted formation of enamine **280**.

2.4.2. Thionation of a tertiary lactam

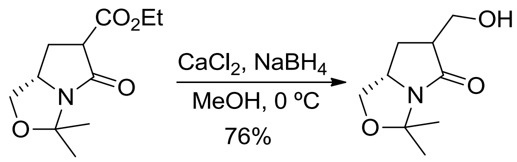
The inability to form the required enamine isomer following *S*-alkylation of secondary thiolactams **254** and **272** meant that work carried out on the thionation of a suitable tertiary lactam had to be revisited. A thiolactam fused to an oxazolidine was an attractive target because it would provide a higher degree of stereocontrol in the thio-Claisen rearrangement than a benzyl ether. This is due to the oxazolidine being constrained and therefore unable to adopt a conformation where the steric bulk is moved away from the thiolactam.

As outlined in the strategy in Scheme 105, a thiolactam with an ester substituent in the α-position was required to form the piperidine ring following the thio-Claisen rearrangement. We decided to install the ester substituent before thionating and thus, the acylation of lactam **211** was carried with diethyl carbonate, furnishing ester **281**.[18] Previous attempts at thionating lactam **211** with Lawesson's reagent led to incomplete reactions. Thionation with P_4S_{10} gave the most favorable conversion, a 1:1 mixture of lactam and thiolactam and the reaction was very clean in comparison to previous attempts at thionating **211**. Disappointingly, thionation of α-acylated lactam **281** using P_4S_{10} in toluene at reflux led to a complex mixture. Thionation was attempted with Lawesson's reagent in toluene at 85 °C, which also gave a complex mixture (Scheme 111).



Scheme 111: α-acylation of **211** sucessfully gave lactam **281**. Thionation of **281** was unsuccessful.

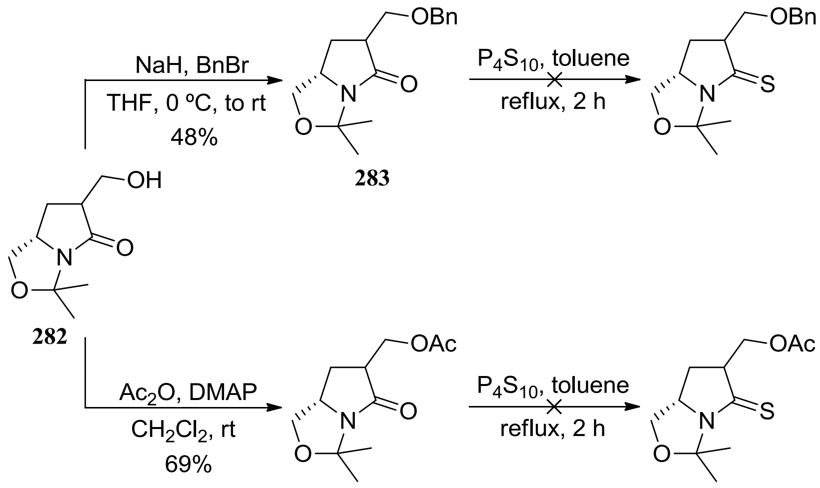
Increased steric hindrance around the amide group or possibly the electron-withdrawing nature of the ester substituent could have been responsible for the unsuccessful thionation. Reduction of the ester group to a hydroxymethyl group could alleviate this problem. The resultant alcohol would be protected, followed by thionation. Ester **281** was reduced with $Ca(BH_4)_2$, which was formed *in situ* from $CaCl_2$ and $NaBH_4$ (Scheme 112).[124]



281 **282**

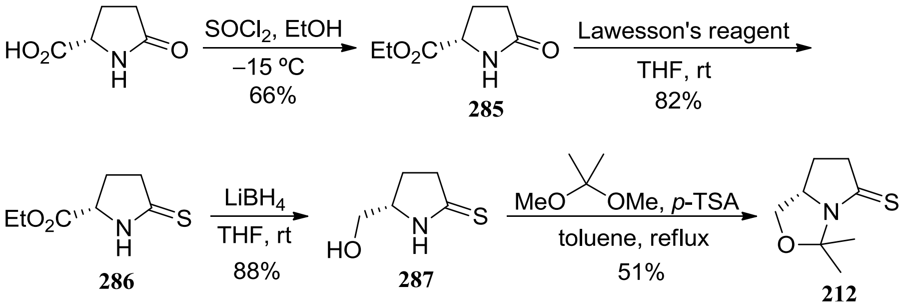
Scheme 112: Reduction of ester **281**.

Alcohol **282** was converted to benzyl ether **283** with BnBr and to acetate **284** using Ac_2O. Attempts were made to convert the amide groups of both **283** and **284** to their respective thiolactam groups using P_4S_{10}, however in both cases a complex mixture was observed (Scheme 113).



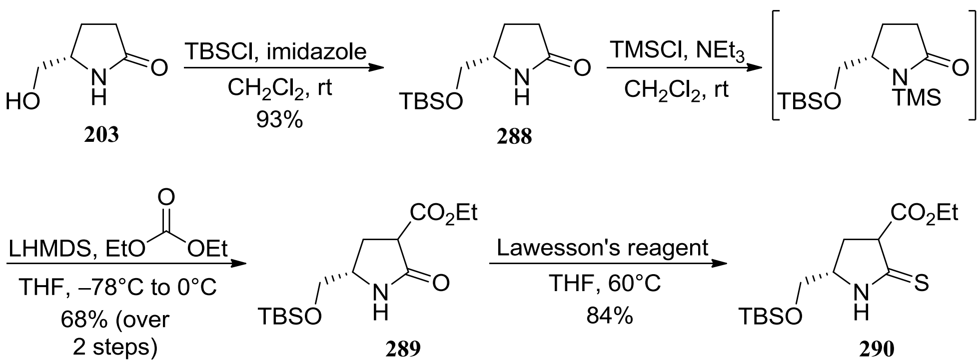
Scheme 113: Attempted thionation of benzyl ether **283** and acetate **284**.

As the thionation of the tertiary lactam had been unsuccessful, changing the order of steps to thiolactam **212** was considered, with the thionation of a lactam coming before the protection to form the isopropylidene group. This strategy began with the conversion of (*S*)-pyroglutamic acid to ethyl ester **285**. This was carried out by forming the acid chloride with $SOCl_2$, which reacted *in situ* with EtOH to form **285**.[125] Ethyl ester **285** was thionated at ambient temperature with Lawesson's reagent to yield thiolactam **286**.[126] The ester functionality was reduced to a hydroxyl group using $LiBH_4$.[127] The resultant product was water soluble, therefore the reaction mixture was purified without work-up, which gave pyrrolidine-2-thione **287**. Tertiary thiolactam **212** was successfully synthesised employing the conditions used to synthesise lactam **211** (Scheme 114).



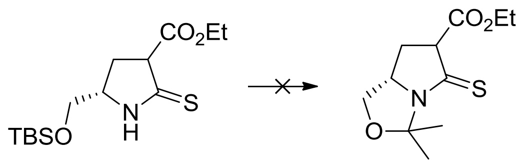
Scheme 114: Alternative synthesis of thiolactam **212**.

Having shown that a secondary thiolactam such as **287** could be converted to acetonide **212**, we attempted to employ this strategy in the synthesis of a similar compound with a substituent α-to the thiocarbonyl group. The alcohol functionality of (*S*)-pyroglutaminol was protected as TBS ether **288** using TBSCl.[128] The amide group was protected using TMSCl with NEt_3 and immediately subjected to an acylation, using diethyl carbonate and LHMDS. The TMS group was removed upon workup, thus successfully giving unprotected lactam **289**, in a good yield over 2 steps.[129] Conversion to thiolactam **290** was effected using Lawesson's reagent (Scheme 115).



Scheme 115: Synthesis of thiolactam **290**.

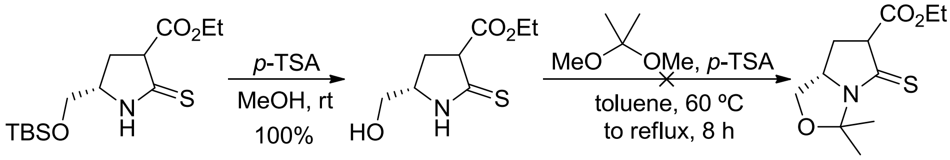
The deprotection/isopropylidene protection was attempted using a catalytic amount of *p*-TSA in neat dimethoxypropane, which gave a complex mixture (Scheme 116). The reaction was repeated with a removal of the TBS group again using *p*-TSA in MeOH, followed by a solvent swap to dimethoxypropane and heating to reflux, also resulting in decomposition.



290

Scheme 116: Attempts at synthesising the isopropylidene *N*,*O*-acetal led to decomposition.

The one pot deprotection/isopropylidene protection was unsuccessful, and so a sequential procedure was considered, which involved the isolation of the alcohol following deprotection (Scheme 117). TBS deprotection was carried out in MeOH with *p*-TSA, which gave alcohol **291** in a quantitative yield.[130] The isopropylidene protection was attempted, which unfortunately led to a complex mixture.



290 **291**

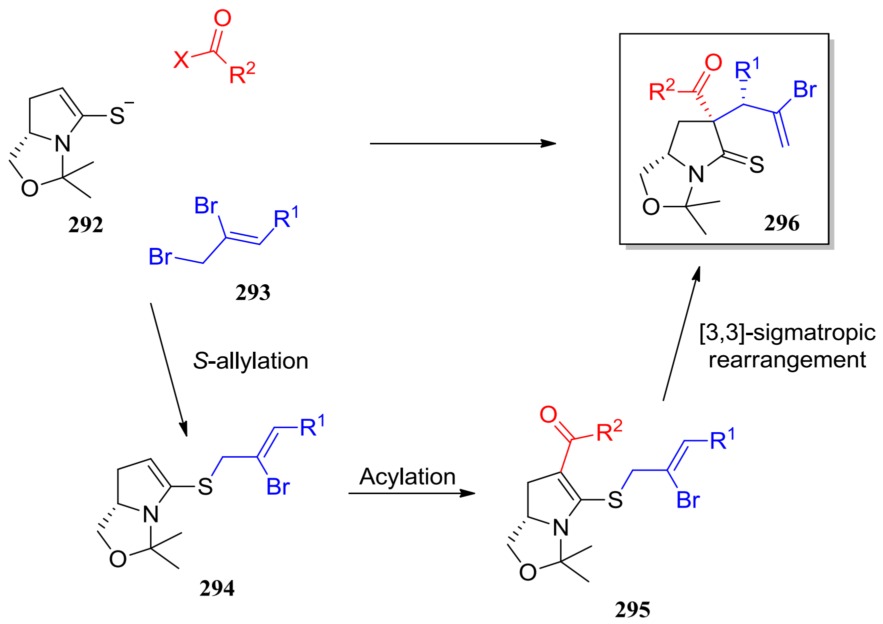
Scheme 117: A sequential procedure was also unsuccessful.

As we had previously synthesised bicyclic thiolactam **212**, we next considered carrying out an α-acylation of this compound. Duhamel *et al*. have shown that α-acylations of thioamides can be carried out using magnesium diisopropylamide, which is formed *in situ* from EtMgBr and diisopropylamine.[131] However under these conditions acylation of thiolactam **212** diethylcarbonate led to the recovery of starting material. The reaction was also attempted using LHMDS and diethylcarbonate, which gave a similar result.

2.5. Development of a three component one-pot acylation/thio-Claisen rearrangement

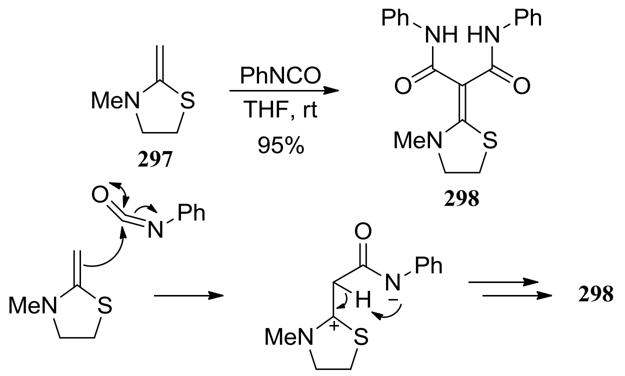
Although the desired 5,5-bicyclic thiolactam **212** had been synthesised, construction of an acylated variant had been unsuccessful. A modification to the current strategy was considered, which involved conversion of the tertiary thiolactam to an *N,S*-ketene acetal *via S*-alkylation with an allylic bromide. The highly electron rich alkene of the resultant *N,S*-ketene acetal could be sufficiently nucleophilic to allow for an α-acylation.

This modified strategy is further explained in Scheme 118, which would begin with a deprotonation of thiolactam **212**, forming thioenolate **292**. This would be alkylated with allylic bromide **293** to give *N,S*-ketene acetal **294**. An acylation of **294** would give rearrangement precursor **295**. Finally, heating to effect the sigmatropic rearrangement would give substituted thiolactam **296**, completing a three component, one-pot acylation/thio-Claisen rearrangement. It should be noted that the acylation of **294** has to be faster than its rearrangement to give the desired product.



Scheme 118: Three component one-pot acylation/thio-Claisen rearrangement. *S*-alkylation of thioenolate **292** would give **294**. Acylation followed by a sigmatropic rearrangement would give the thio-Claisen adduct.

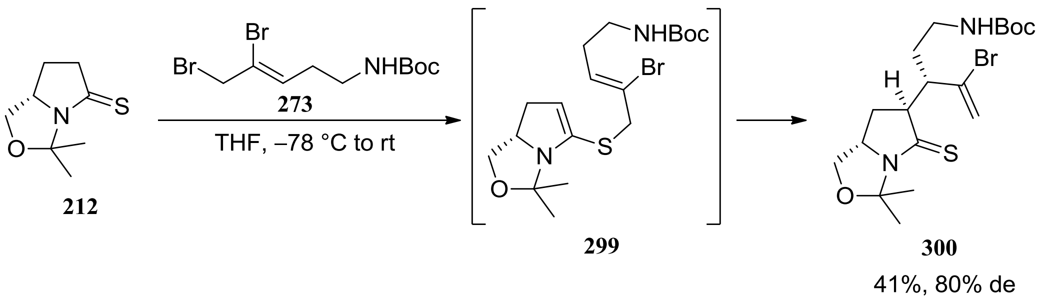
Various electrophiles including chloroformates,[132] anhydrides[133] and acyl chlorides[133] have been found to acylate *N,S*-ketene acetals. Zhou *et al*. have shown that *N,S*-ketene acetal **297** can undergo a double acylation with an excess of phenyl isocyanate under mild conditions, giving **298** in an excellent yield (Scheme 119).[134] Acylating with phenyl isocyanate avoids the formation of acidic by-products, as the nitrogen atom abstracts a proton following acylation.



Scheme 119: Double acylation of an *N,S*-ketene acetal with phenyl isocyanate.

2.5.1. Preparation of an *N,S*-ketene acetal

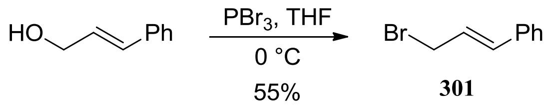
Work on this strategy commenced with an investigation into the formation of a suitable *N,S*-ketene acetal (Scheme 120). Thiolactam **212** was deprotonated with *n*-BuLi to form the thioenolate, which was then allylated with the previously synthesised allylic bromide **273**. Unfortunately, *N,S*-ketene acetal **299** rearranged to thiolactam **300**. It was deduced from this result that the thio-Claisen rearrangement had taken place at ambient temperature or lower.



Scheme 120: Attempted synthesis of *N,S*-ketene acetal **299** using allylic bromide **273**.

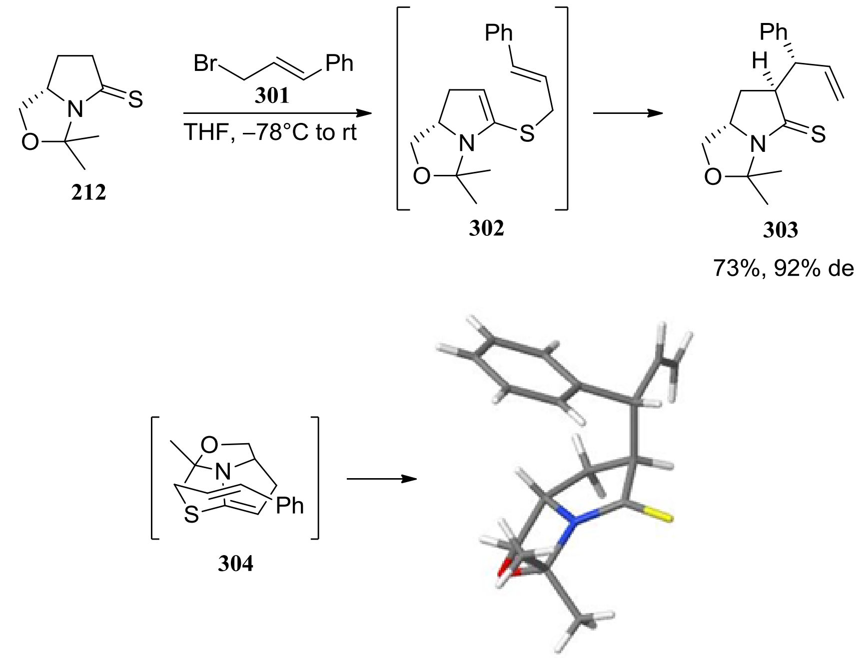
To investigate the three-component reaction with a more readily accessible and cost effective compound than **273**, cinnamyl bromide would be used instead of allylic bromide

301. Cinnamyl bromide was synthesised from cinnamyl alcohol with PBr_3 (Scheme 121).[135]



Scheme 121: Synthesis of cinnamyl bromide.

The *S*-allylation was repeated with allylic bromide **301** used instead of **273**. Disappointingly, *N*,*S*-ketene acetal **302** could not be isolated, and instead thio-Claisen adduct **303** had formed. The structure of **303** was confirmed by X-ray crystallography,[136] which also confirmed the stereochemical configuration of the product, arising from what was expected to be the favoured transition state **304** (Scheme 122). This reaction demonstrates the high degree of facial selectivity imparted by the isopropylidene acetal.



Scheme 122: Isolation of *N*,*S*-ketene acetal **302** was unsuccessful. **302** underwent a thio-Claisen rearrangement to give **303**. X-ray crystal structure confirmed the structure of **303**.

In an attempt to isolate *N*,*S*-ketene acetal **302**, allyl bromide **301** was added at –40 °C following deprotonation of thiolactam **212**. The reaction was warmed to –20 °C over 30 minutes, then quenched with 1M NaOH solution and the crude product was immediately analysed by ^{1}H NMR spectroscopy (Figure 10). The spectrum showed a compound which was identified as *N,S*-ketene acetal **302**, although it began to rapidly rearrange at room temperature to form thiolactam **303** (Figure 11).

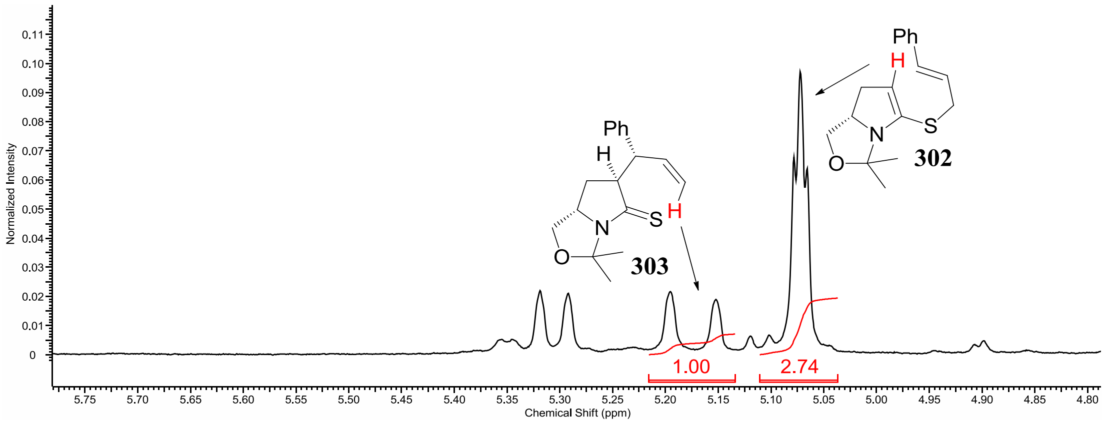


Figure 10: ^{1}H NMR spectrum taken approximately 5 minutes after work up and shows the presence of the desired *N,S*-acetal **302** in a 2.7:1 ratio with the thio-Claisen adduct.

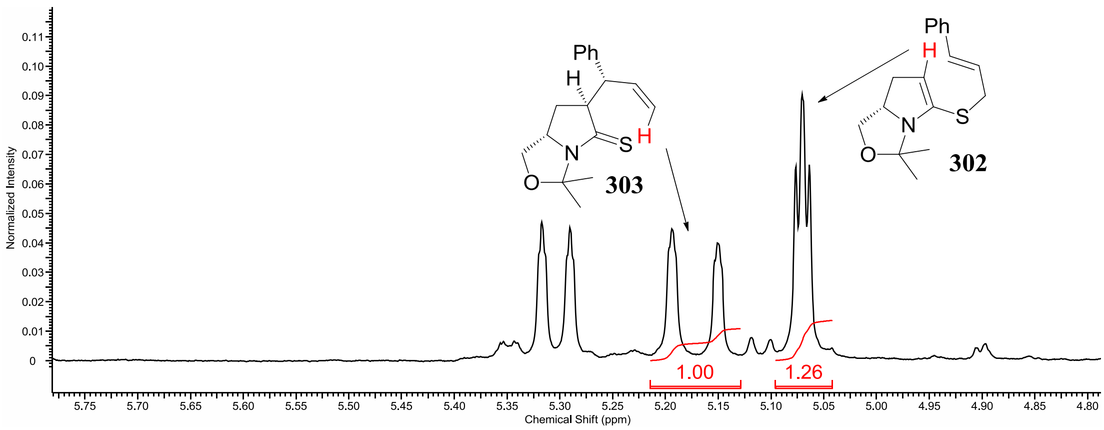
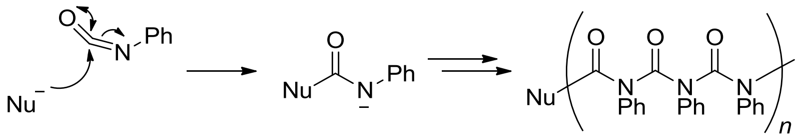


Figure 11: ^{1}H NMR spectrum taken approximately 10 minutes after work up showing a 1.3:1 ratio of **302** to **303**, confirming the *N,S*-ketene acetal rearranges rapidly at room temperature.

2.5.2. Attempts at a one pot acylation/thio-Claisen rearrangement using cinnamyl bromide

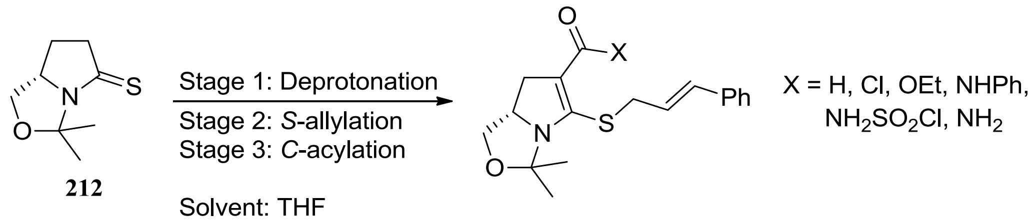
This result was promising, as it showed that *N,S*-ketene acetal **302** has an appreciable lifetime in solution, giving rise to the possibility of an *in situ* acylation. Attempts at the one pot acylation/thio-Claisen rearrangement are summarised in Table 11. The general procedure involved an initial deprotonation of thiolactam **212** with either *n*-BuLi or LHMDS, followed by the addition of cinnamyl bromide and the acylating agent. The first effort involved the use of LHMDS as base and ethyl chloroformate as the acylating agent (entry 1). Unfortunately, the acylation was unsuccessful and instead the rearranged product, thiolactam **303**, was observed. Increasing the amount of ethyl chloroformate to five equivalents had no effect on the reaction and led to the formation of **303** (entry 2). Change of the acylating agent and base to formic acetic anhydride and *n*-BuLi respectively also led to the formation of thiolactam **303** (entries 3 and 4).

The acylation was next attempted with phenyl isocyanate. A precipitate formed following the addition of the isocyanate, and again the non-acylated thiolactam **303** was observed (entry 5). Lowering the temperature of addition of the acylating agent (entry 6), led to the same result with the formation of the unknown precipitate. A change in the sequence of addition was next attempted (entry 7). The cooling solution of the *N*,*S*-ketene acetal was added to neat isocyanate and led to the instantaneous formation of the precipitate upon the addition of only a few drops of the *N*,*S*-ketene acetal. It was discerned from this observation that a polymerisation of the acylating agent was taking place (Scheme 123).



Scheme 123: Polymerisation of phenyl isocyanate.

It was presumed that excess base present in the solution was initiating the polymerisation.[137] However, reducing the amount of base to 0.9 equivalents had no effect on the outcome of the reaction and polymerisation was observed along with rearranged product **303** (entry 8). Increasing the electrophilicity of the acylating agent could favour acylation over the competing polymerisation. Therefore the acylation was attempted with chlorosulfonyl isocyanate, which led to the decomposition of the starting material (entries 9 and 10). Deprotection of the acetonide group and some decomposition was observed with trichloroacetyl isocyanate (entry 11). Phosgene also gave a similar result, with no observed rearrangement or acylation and some decomposition (entry 12).



212

Entry	Stage 1	Stage 2	Stage 3	Product observed
1	LHMDS (1.2 eq), 0 °C for 45 mins	**301** (1.1 eq), –78 °C for 1 h	EtOCOCl (1.1 eq), –78 °C for 30 mins then warmed to rt	**303**
2	LHMDS (1.2 eq), 0 °C for 30 mins	**301** (1.1 eq), –20 °C for 1 h	EtOCOCl (5 eq), –20 °C for 1 h then warmed to rt	**303**
3	*n*-BuLi (1.05 eq), 0 °C for 30 mins	**301** (1.1 eq), –20 °C for 40 mins	HCOOAc (1.2 eq), –20 °C for 1 h then warmed to rt	**303**
4	*n*-BuLi (1.05 eq), 0 °C for 30 mins	**301** (1.1 eq), 0 °C for 30 mins	HCOOAc (25 eq), 0 °C for 1 h then warmed to rt	0[a]
5	*n*-BuLi (1.05 eq), 0 °C for 15 mins	**301** (1.1 eq), 0 °C for 30 mins	PhNCO (10 eq), 0 °C for 1 h then warmed to rt	**303**[b]
6	*n*-BuLi (1.05 eq), 0 °C for 15 mins	**301** (1.2 eq), –78 °C for 45 mins	PhNCO (20 eq), –78 °C for 30 mins then warmed to rt	**303**[b]
7	*n*-BuLi (1.05 eq), 0 °C for 15 mins	**301** (1.1 eq), –78 °C for 30 mins	Allylated product solution (at –78 °C) added to PhNCO (20 eq)	**303**[b]
8	*n*-BuLi (0.9 eq), 0 °C for 15 mins	**301** (1.1 eq), –78 °C for 30 mins	Allylated product solution (at –78 °C) added to PhNCO (20 eq)	**303**[b]
9	*n*-BuLi (1.05 eq), 0 °C for 15 mins	**301** (1.1 eq), 0 °C for 30 mins	$ClSO_2NCO$ (1.1 eq), 0 °C for 1 h then warmed to rt	0[a]
10	*n*-BuLi (1.05 eq), 0 °C for 15 mins	**301** (1.1 eq), 0 °C for 30 mins	$ClSO_2NCO$ (10 eq), 0 °C for 1 h then warmed to rt	0[a]
11	*n*-BuLi (1.05 eq), 0 °C for 15 mins	**301** (1.1 eq), –78 °C for 45 mins	Cl_3CONCO (10 eq), –78 °C for 45 mins then warmed to rt	0[a,c]
12	*n*-BuLi (1.05 eq), 0 °C for 15 mins	**301** (1.1 eq), –78 °C for 45 mins	$COCl_2$ (1 eq), –78 °C for 1 h then warmed to rt	0[a,c]

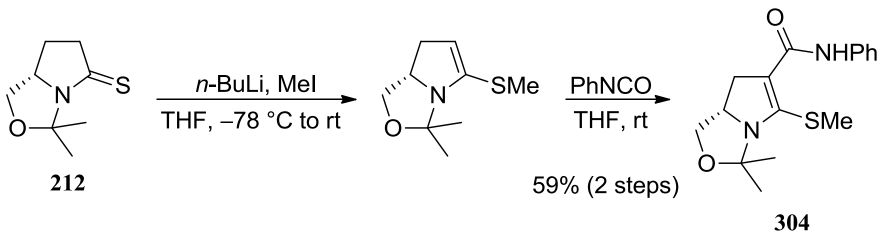
[a] decomposition [b] precipitate observed [c] deprotection of the isopropylidene acetal.

Table 11: Attempts at a one pot acylation/thio-Claisen rearrangement using cinnamyl bromide and various electrophiles.

2.5.3. Preparation of an *N,S*-ketene acetal using a *Z*-allylic bromide

After carrying out an exhaustive investigation into the acylation of *N,S*-ketene acetal **302**, an alteration to the strategy was needed. Thiolactam **212** contains a key structural feature; a fused oxazolidine ring, which allows for a highly stereoselective thio-Claisen rearrangement. However, the additional ring strain from the bicyclic system could mean the nitrogen lone pair is out of plane. This would have a significant impact on the reactivity of the *N,S*-ketene acetal, as the lack of participation of the lone pair would lower the nucleophilicity of **302**, thus preventing the acylation from taking place.

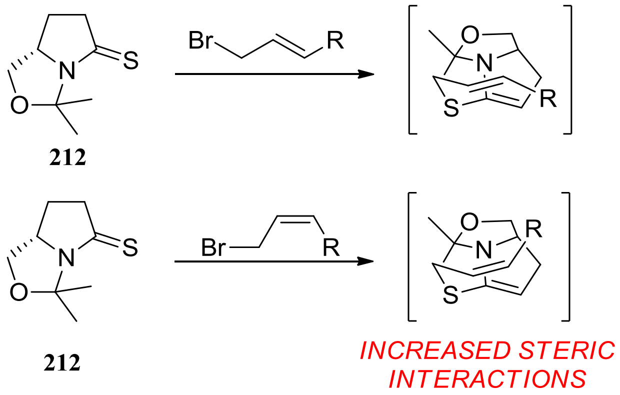
To test this hypothesis, an *S*-alkylation of thiolactam **212** was carried out with MeI. The lack of the double bond in the *S*-methylated compound would prevent the thio-Claisen rearrangement from taking place and would allow for the isolation of *N,S*-ketene acetal **302**. Of the acylating agents used previously, phenyl isocyanate was the most desirable as it would not require additional base to neutralise any acidic by-products. The *S*-methylation was carried out with a deprotonation of thiolactam **212** followed by addition of MeI. The resultant product was submitted immediately to the acylation, allowing for the successful synthesis of amide **304** under mild conditions (Scheme 124).



Scheme 124: Successful acylation of an *N,S*-ketene acetal.

This result confirmed that an acylation could indeed be carried out on an *N,S*-ketene acetal derived from thiolactam **212**. The next objective was to carry out a modification which would ensure that the reaction of the allylic ketene acetal with an electrophile was faster than its sigmatropic rearrangement.

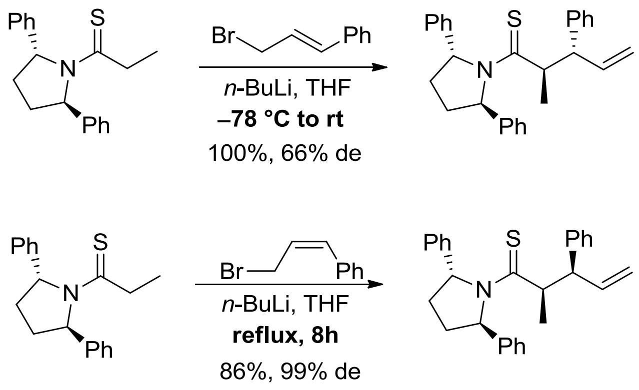
Evaluating the reactive conformations for the thio-Claisen rearrangement in Scheme 125, it can be seen that greater steric interactions are experienced between the R group and the pyrrolidine ring when thiolactam **212** is allylated with a *Z*-allylic bromide. This could have the effect of increasing the activation energy of the rearrangement, which could mean the acylation of the allylic ketene acetal could occur before the sigmatropic rearrangement.



Scheme 125: Comparison of the reactive conformations for the thio-Claisen rearrangement when a *Z* or an *E* allylic bromide is used.

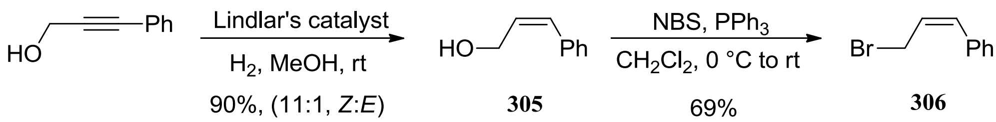
Rawal and co-workers have carried out extensive investigations into highly diastereoselective thio-Claisen rearrangements of functionalised thioamides using various allylic bromides.[138] An interesting trend was reported in their work; the use of *E*-allylic bromides allowed for a thio-Claisen rearrangement to be carried out at room temperature. However, when *Z*-allylic or tetrasubstituted allylic bromides were used, the reactions required heating to effect the rearrangement.

The example in Scheme 126 demonstrates the difference in reactivity between *E* and *Z* allylic bromides. When the allylation was carried out with *E* cinnamyl bromide the rearrangement took place at ambient temperature. However, when *Z* cinnamyl bromide was used, prolonged heating was required to effect the rearrangement. It should also be noted that higher degrees of stereocontrol were obtained with *Z* allylic bromides.



Scheme 126: Work carried out by Rawal and co-workers showed that when Z-allyic bromides were used, heating was required to effect the sigmatropic rearrangement.

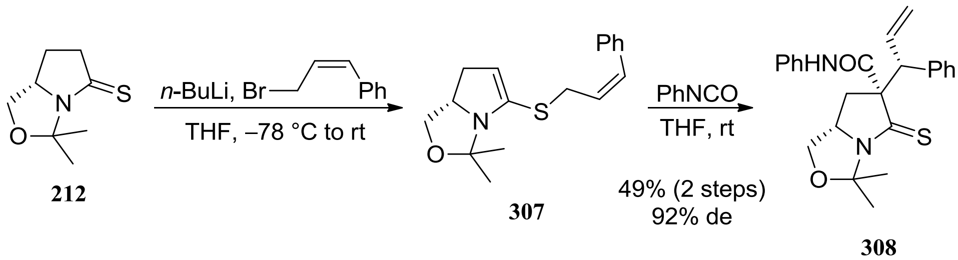
To test this hypothesis with thiolactam **212**, *Z*-cinnamyl bromide was synthesised by carrying out a *Z*-selective reduction of phenylpropargyl alcohol using Lindlar's catalyst in an atmosphere of H_2.[139] The *Z* allylic alcohol **305** was subsequently treated with NBS/PPh_3, giving *Z*-cinnamyl bromide **306** (Scheme 127).[140]



305 **306**

Scheme 127: Synthesis of *Z*-cinnamyl bromide.

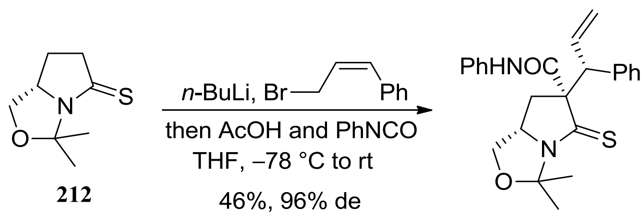
With *Z*-cinnamyl bromide in hand, the *S*-alkylation of thiolactam **212** was attempted. The thiolactam was deprotonated with *n*-BuLi, and then treated with the allylic bromide. Pleasingly, *N*,*S*-ketene acetal **307** was isolated with no observed rearrangement, although some decomposition was observed. Nevertheless, the isolated *N*,*S*-ketene acetal was acylated with phenyl isocyanate under mild conditions. Gratifyingly, we found that not only was the acylation successful, the thio-Claisen rearrangement had also proceeded without the need for heating, to give thiolactam **308** (Scheme 128). Additionally, the stereoselectivity (de: 92%, determined by ^{1}H NMR) compared well to what was obtained in the synthesis of **303** (de: 92%, determined by ^{1}H NMR).



212 307 308

Scheme 128: Acylation/thio-Claisen rearrangement.

It was felt that this protocol could be improved further with a one-pot procedure. The problems encountered with polymerisation of phenyl isocyanate could be circumvented by quenching the reaction with a small amount of acid following *S*-alkylation. The formation of *N,S*-ketene acetal **307** was repeated, carrying out the deprotonation with 0.98 equivalents of *n*-BuLi. Following the addition of allylic bromide **306**, the reaction was treated with 6 × 10^{-5} equivalents of acetic acid followed immediately with phenyl isocyanate. No precipitate was observed following the addition of the acylating agent and the reaction was stirred for 18 h. Pleasingly, thiolactam **308** was isolated and we had thus successfully carried out a one-pot three-component acylation/thio-Claisen rearrangement (Scheme 129). In this reaction, a single pre-existing chiral centre directs the sigmatropic rearrangement in an extremely stereoselective fashion, forming two contiguous stereocentres, one of which is a quaternary carbon.

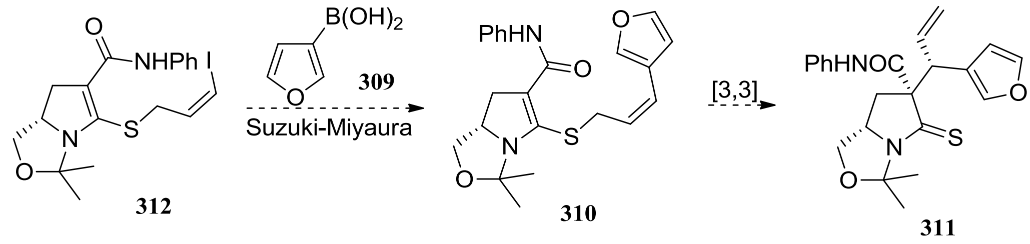


212 308

Scheme 129: One pot three component acylation/thio-Claisen rearrangement.

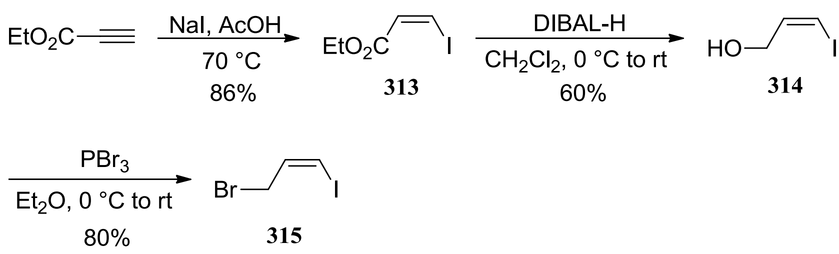
2.5.4. Application of the acylation/thio-Claisen rearrangement to the synthesis of the ABCD ring system

This promising result prompted the formulation of a new strategy that would allow for its application to the synthesis of the ABCD ring system. It was unfortunate that the selective synthesis of *Z*-allylic furan **237** had been unsuccessful, as we would have been able to substitute it directly for *Z*-cinnamyl bromide in the one-pot procedure. Instead, we chose to investigate the *S*-alkylation of a compound containing a vinyl iodide and attempt a Suzuki-Miyaura coupling with furan-3-boronic acid **309** giving compound **310**. This should then rearrange to give thiolactam **311** (Scheme 130).



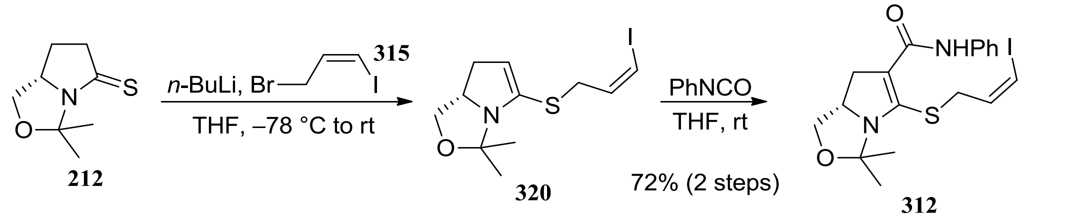
Scheme 130: Application of the one pot protocol to the synthesis of the ABCD ring system.

Work on this strategy commenced with the synthesis of a suitable allylic bromide, which would be used to construct *N*,*S*-ketene acetal **312**. *Z*-vinylic iodide **313** was synthesised from ethyl propiolate and NaI.[141] The ester group was reduced with DIBAL-H to furnish allylic alcohol **314**.[142] Finally, reaction with PBr_3 yielded the desired allylic bromide **315** containing a vinyl iodide moiety (Scheme 131).[143]



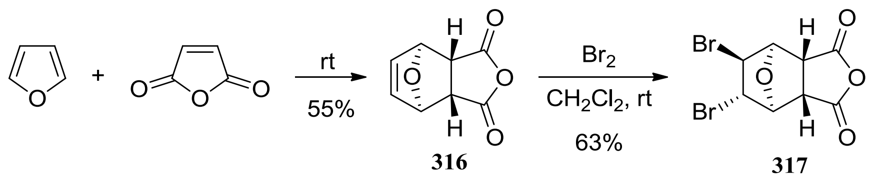
Scheme 131: Synthesis of *Z*-allylic bromide **315**.

Using allylic bromide **315** and phenyl isocyanate with the conditions used to synthesise acylated *N*,*S*-ketene acetal **304**, vinyl iodide **312** was successfully synthesised (Scheme 132). We were delighted to find that **312** proved stable as there is potential for it to undergo sigmatropic rearrangement



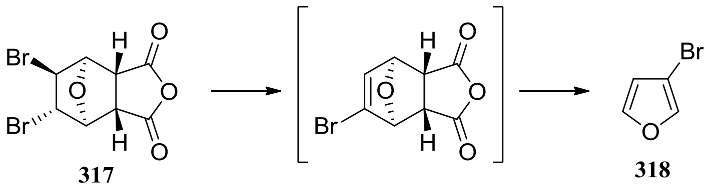
Scheme 132: *S*-allylation followed by acylation of thiolactam **212** with allylic bromide **315** and phenyl isocyanate.

Attention now turned to the synthesis of the boronic acid. The bromide precursor was synthesised following Curtis' procedure.[144] A Diels-Alder reaction of furan with maleic anhydride furnished **316**. Diels-Alder adduct **316** was subsequently brominated, which gave **317** (Scheme 133).



Scheme 133: Synthesis of 3-bromofuran precursor.

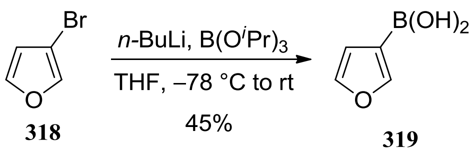
To convert **317** to the required 3-bromofuran, a dehydrobromination followed by a retro Diels-Alder reaction was attempted (Table 12). The dehydrobromination was first attempted using *t*-BuOK (entry 1), which led to a recovery of starting material. The next attempt used KOH, which gave an unidentified product (entry 2). Curtis was able to effect the dehydrobromination/ retro Diels-Alder reaction by heating **317** in quinoline at 140 °C. However, heating **317** in quinoline at 150 °C led to the recovery of starting material (entry 3). After heating a mixture of **317** in quinoline to 215 °C, bromide **318** was isolated following distillation (entry 5).



Entry	Conditions	Yield
1	*t*-BuOK (1.1 eq), THF, rt, 5 h	0[a]
2	KOH (3 eq), MeOH, reflux, 3 h	0[b]
3	Quinoline, 150 °C, 3 h	0[a]
4	Quinoline, 170 °C, 6 h	0[a]
5	Quinoline, 215 °C, 1 h	28%
[a] starting material observed [b] unidentified product.		

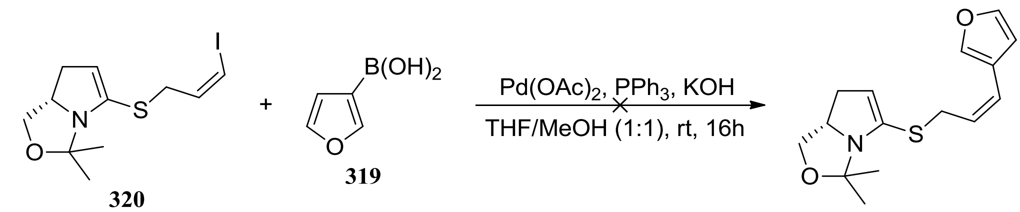
Table 12: Attempts at synthesising 3-bromofuran *via* a dehydrobromination/retro Diels-Alder reaction.

The 3-bromofuran was converted to the required boronic acid, following the procedure outlined by Beaulieu.[145] Lithium-halogen exchange followed by reaction with triisopropyl borate and hydrolysis furnished boronic acid **319** (Scheme 134).



Scheme 134: Conversion of 3-bromofuran to boronic acid **319**.

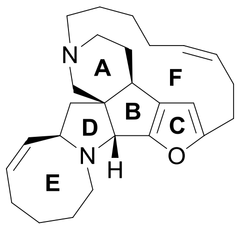
Following the successful synthesis of boronic acid **319**, the Suzuki-Miyaura coupling with **320** was attempted with $Pd(OAc)_2$ and PPh_3 (Scheme 135).[146] Unfortunately we were unable to effect this transformation and found that the *N*,*S*-ketene acetal had hydrolysed to the lactam. At this point, time constraints precluded any further investigation of this coupling reaction.



Scheme 135: Attempted Suzuki coupling of vinyl iodide **320** with boronic acid **319**.

3. CONCLUSIONS AND FUTURE WORK

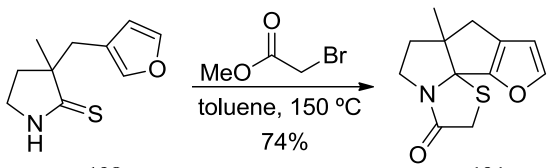
This thesis has described the various attempts made at constructing the BCDE and ABCD ring systems of nakadomarin A. The two primary synthetic strategies involved the use of a thio-Claisen rearrangement to establish two of the four stereocentres, and an iminium ion/furan ring cyclisation to form the carbocyclic B ring.



7

Figure 12: Nakadomarin A with rings labelled

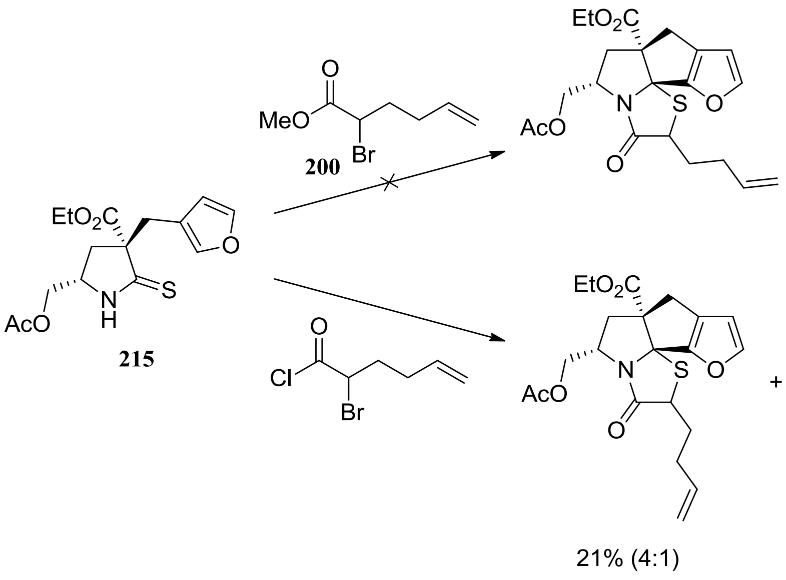
Synthetic studies towards the core ring system began with the investigation of the cyclisation of a furan ring onto an iminium ion, which would be derived from a thioamide group. After exploring various approaches, a cyclisation of a furan ring onto a thio *N*-acyliminium ion was successfully carried out in model system **198**, which gave tetracycle **191**. The iminium ion was generated through a sequential *S*-alkylation and *N*-acylation of an unprotected thiolactam with an α-bromo ester (Scheme 136).



198 **191**

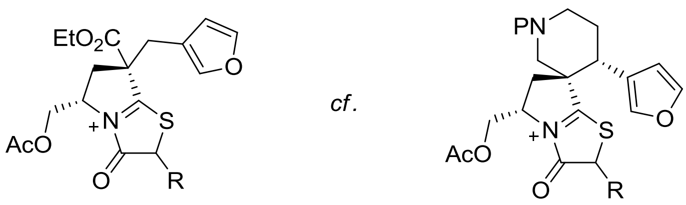
Scheme 136: Successful attempt at a thio N-acyliminium ion/furan cyclisation.

Unfortunately, application of this methodology to the synthesis of the BCDE ring system was unsuccessful. The thio *N*-acyliminium ion/furan cyclisation was attempted on functionalised thiolactam **215** with secondary α-bromo ester **200**, which led to no reaction (Scheme 137). Change of α-bromo ester **200** to the more reactive acyl chloride variant led to unsatisfactory product mixtures.



Scheme 137: Using a secondary bromoester in the thio *N*-acyliminium ion/furan cyclisation led to recovery of starting material. When the reaction was carried out with an acyl chloride, an unsatisfactory product mixture was obtained.

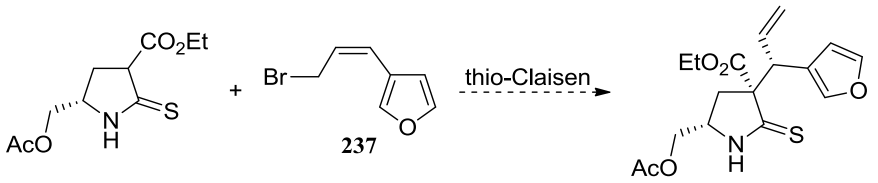
Increasing the rigidity in the molecule by synthesising the piperidine ring before carrying out the cyclisation could improve the product distribution, as the furan ring would be in close proximity to the iminium ion (Figure 13)



234 **235**

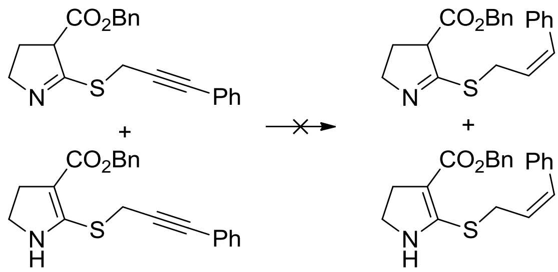
Figure 13: Comparison of iminium ion **234** with iminium ion **235** which contains the key piperidine ring needed to improve the selectivity of the cyclisation.

To achieve this, a thio-Claisen rearrangement was targeted, which would give a product with the piperidine ring precursor groups (Scheme 138). However, attempts at synthesising allylic bromide **237** led to a mixture of *Z* and *E* isomers.



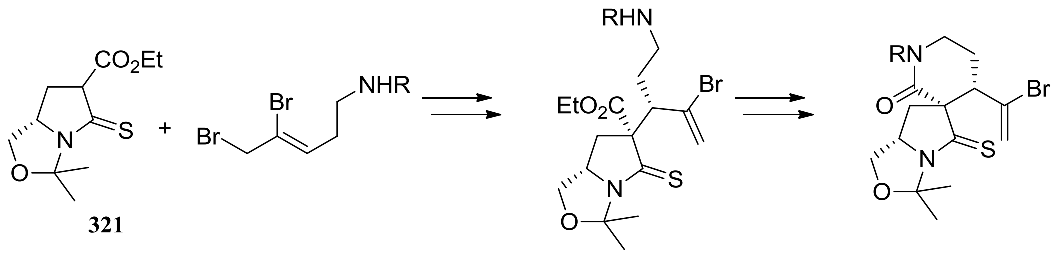
Scheme 138: A thio-Claisen rearrangement with allylic bromide **237** would give a product with the piperidine pre-cursor groups.

To circumvent this, a thiolactam would be *S*-alkylated with a propargyl bromide, which would then be reduced selectively to give a *Z*-allylic thiol. A mixture of *N,S*-ketene acetal and thioimidate was synthesised, however attempts at reducing the alkyne were unsuccessful (Scheme 139).



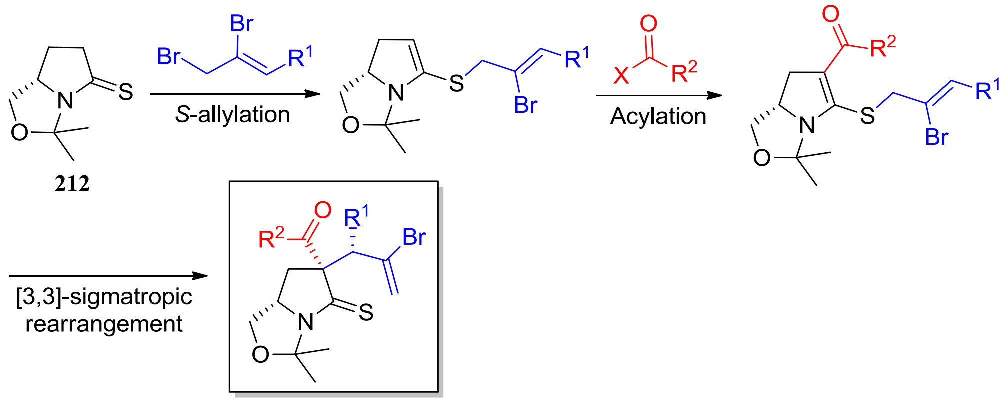
Scheme 139: Attempts at a Z-selective reduction using Lindlar's catalyst and *in situ* generation of diimide were unsuccessful.

To bypass issues with isomeric mixtures, a tertiary thiolactam was synthesised, which would be submitted to a thio-Claisen rearrangement with a more stable *E*-allylic bromide (Scheme 140). Deprotonation of thiolactam **321** would give a thioenolate, which could undergo *S*-allylation followed by the sigmatropic rearrangement. The previous strategy required the use of a *Z*-allylic bromide, which would give the *anti* diastereoisomer. The terminal alkene would then be used to form the piperidine ring. With an *E*-allylic bromide, the *syn* product would be obtained and the terminal alkene would be used to construct the furan ring.



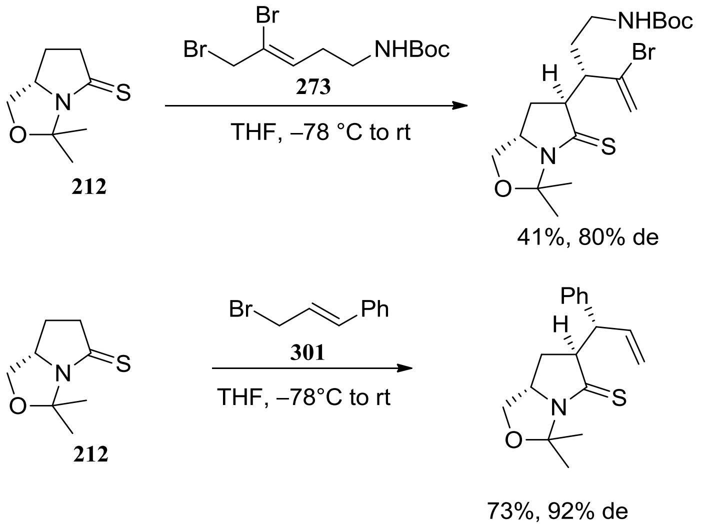
Scheme 140: A thio-Claisen rearrangement with an *E*-allylic bromide would give the *syn* product and the terminal alkene would be used to construct the furan ring.

As shown in Scheme 140, a thiolactam with a substituent in the α-position was required to form the piperidine ring. Attempts at synthesising an α-substituted tertiary thiolactam were unsuccessful, thus the strategy was modified to allow for an acylation of an *N*,*S*-ketene acetal, formed from *S*-alkylation with an allylic bromide. The acylated ketene acetal could then undergo a thio-Claisen rearrangement (Scheme 141).



Scheme 141: Three component one-pot acylation/thio-Claisen rearrangement.

S-Alkylation of thiolactam **212** with *E*-allylic bromides **273** and **301** led to the formation of the thio-Claisen adducts at room temperature (Scheme 142). A one pot method was attempted which involved the formation of the *N*,*S*-ketene acetal followed by an *in situ* acylation. This protocol was attempted with many acylating agents, all of which were unsuccessful.



Scheme 142: Attempts at isolating the *N*,*S*-ketene acetal following the *S*-alkylation of **212** were unsuccessful. Thio-Claisen adducts were obtained instead.

Increasing the steric hindrance of the transition state of the thio-Claisen rearrangement could allow for the isolation of the *N*,*S*-ketene acetal at room temperature (Figure 14).

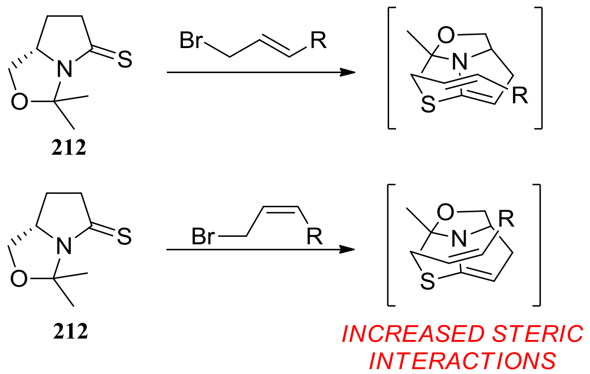
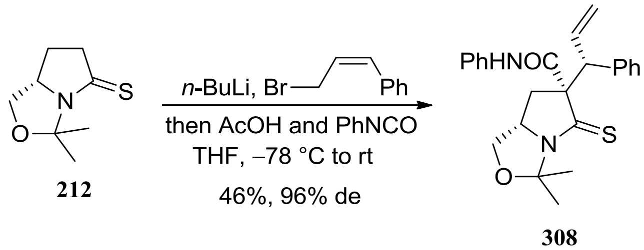


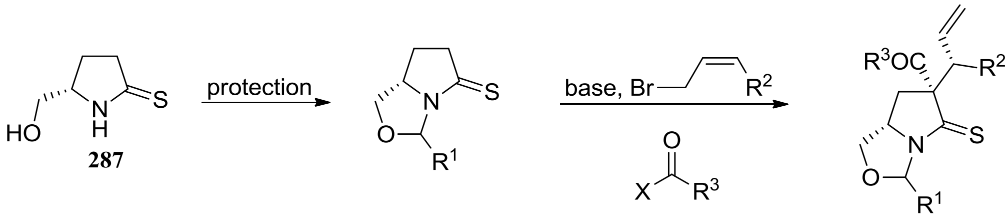
Figure 14: A comparison of the transition states when *Z* and *E*-allylic bromides are used.

Thus, thiolactam **212** was allylated with *Z*-cinnamyl bromide and the resultant *N*,*S*-ketene acetal was acylated and underwent a sigmatropic rearrangement to give the desired thiolactam adduct with excellent diastereoselectivity (Scheme 143).



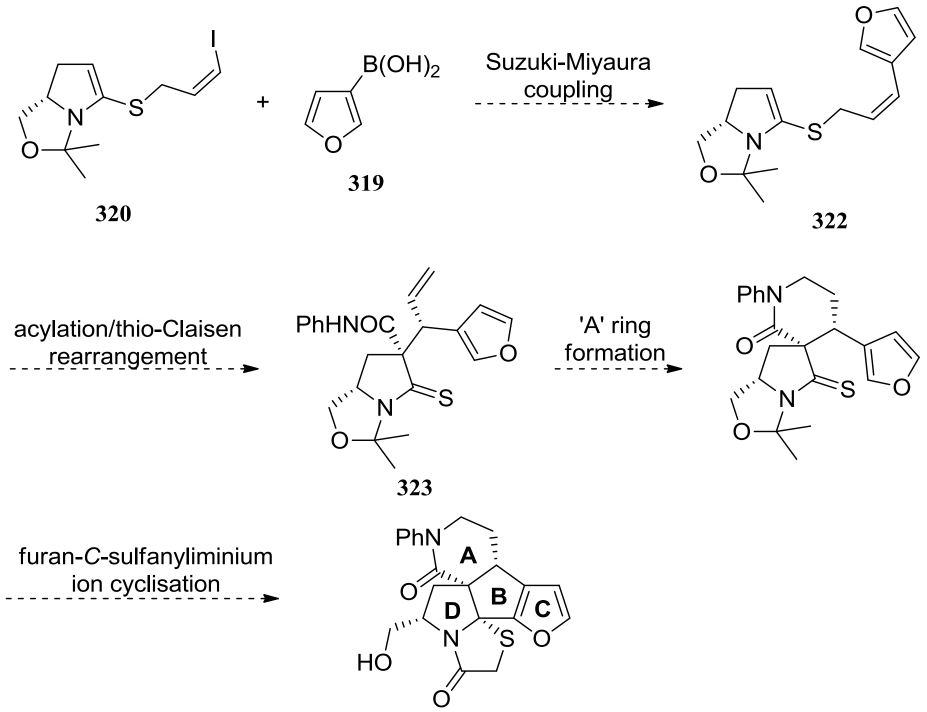
Scheme 143: A successful attempt at a three component one-pot acylation/thio-Claisen rearrangement using a Z-allylic bromide.

With the successful synthesis of thiolactam **308**, a powerful protocol has been developed which allows for the synthesis of highly functionalised thioamide groups and the fused isopropylidene ring was demonstrated to provide excellent stereocontrol in the sigmatropic rearrangement. The scope of this newly developed methodology will be explored through the use of various *Z*-allylic bromides and acylating agents. Further investigations into the stereoselectivity of this reaction will be carried out by a change of the isopropylidene *N*,*O*-acetal, or through the use of an acyclic protecting group (Scheme 144).



Scheme 144: This newly developed methodology allows for the synthesis of highly functionalised thiolactams.

As well as carrying out further investigative studies into the three component one-pot acylation/thio-Claisen rearrangement, efforts will be made to progress the total synthesis of nakadomarin A. The methodology in Scheme 144 will be modified to allow for its application to the synthesis of the ABCD ring system of nakadomarin. The initial strategy will follow on from the work carried out on the Suzuki Miyaura coupling of vinyl iodide **183** and boronic acid **182**. An in-depth screening of conditions for this coupling reaction will be carried out to form *N,S*-ketene acetal **184**. This will be followed by the acylation/thio-Claisen rearrangement to give adduct **185**. Formation of the 6-membered A ring followed by furan-*C*-sulfanyliminium ion cyclisation will give the ABCD ring system of nakadomarin A (Scheme 145).



Scheme 145: Application of the three component one-pot acylation/thio-Claisen rearrangement to the synthesis of the ABCD ring system of nakadomarin A.

4. EXPERIMENTAL

General

All reactions carried out in anhydrous conditions were performed under an argon atmosphere, using flame-dried flasks. TLC analysis was carried out on Merck Kieselgel 60 F254 coated aluminium sheets. Ultra-violet visualisation was performed at 254 nm and the visualised plates were stained with potassium permanganate or CAN.

Solvents

Solvents (CH_2Cl_2, Et_2O, hexane, MeCN, THF, toluene) were obtained from the UCL Chemistry department's anhydrous solvent system, whereby solvents were dried by passing through activated alumina under nitrogen. DMF and DMSO were distilled from CaH_2 and stored over 4 Å molecular sieves.

Reagents

Reagents were purchased from Acros, Alfa Aesar, Aldrich, Avocado, Fisher, Fluka, Lancaster, and were used without further purification, unless otherwise stated. Lawesson's reagent was prepared according to the procedure outlined by Thomsen *et al*.[61] NEt_3 and ^{i}PrNH were distilled from CaH_2 and stored over KOH. Et_3SiH, $BF_3.OEt_2$ and HMDS were distilled prior to use.

Purification

Flash chromatography was carried out using Merck silica gel 60 (40-60 um). Lactams **170** and **171** were purified by a MDAP (mass directed auto preparative) reverse phase HPLC system. The system consisted of a Waters HPLC instrument coupled to a MicroMass ZQ mass spectrometer and a Gilson waste collector. A Waters XBridge™ C_{18} column (100 mm × 30 mm) with a particle size of 5 μm was used. The software used was MicroMass MassLynx. The sample was dissolved in DMSO and eluted with a gradient of 15-55% acetonitrile in 10 mM ammonium bicarbonate solution (adjusted to pH 10 with ammonia solution) over 25 minutes with a flow rate of 40 mL/min. The purification method was denoted as 'High pH Method B' in the user interface.

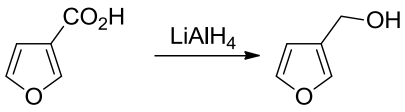
Spectroscopy

^{1}H and ^{13}C NMR were recorded on Bruker AMX-400, AVANCE-500 and AVANCE-600 spectrometers. Chemical shifts (δ) are given in parts per million (ppm), and reported with reference to the solvent peak. The signals are denoted as s = singlet, d = doublet, t = triplet, q = quartet (and combinations thereof), quin = quintet, m = multiplet, br = broad. Coupling constants, *J*, are given in hertz (Hz). COSY, DEPT, HMQC and HMBC were routinely used to aid assignment of spectra. High and low resolution mass spectra were recorded by Mr John Hill and Dr. Lisa Haigh using VG ZAB-SE or ZAB-SE4F instruments operating in modes CI, EI and ES. IR spectra were recorded on a Perkin Elmer Spectrum 100 FTIR (ATR mode).

Miscellaneous

Melting points were measured using a Reichert-Jung Thermovar instrument. Optical rotations were measured on a Perkin Elmer Model 343 Polarimeter. Elemental analyses were carried out by Mrs Jill Maxwell and were recorded on a Perkin Elmer 2400 CHN elemental analyser. X-ray crystallographic structure analysis was carried out by Dr. Peter Horton at the EPSRC National Crystallography Service, Southampton.

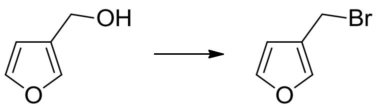
<u>164.</u> Furan-3-ylmethanol



164

Prepared by the method of Wang.[147] A stirred suspension of $LiAlH_4$ (212 mg, 5.58 mmol) in Et_2O (5 mL) was cooled to 0 ºC. The suspension was treated with 3-furoic acid (0.50 g, 4.5 mmol) in Et_2O (5 mL) and stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (10 mL) then stirred for 30 mins at room temperature. The mixture was treated with 10% aq. H_2SO_4 solution and the organic material extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with H_2O (10 mL), brine (10 mL), dried ($MgSO_4$) then concentrated *in vacuo* to give alcohol **1** (323 mg, 74%) as a colourless oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 3322 (O-H), 2933 (C-H), 2882 (C-H); ^{1}H NMR (600 MHz; $CDCl_3$): δ 4.56 (2H, s, $C\underline{H}_2OH$), 6.44 (1H, d, *J* 0.9 Hz $CH_2CC\underline{H}$), 7.40 (1H, t, *J* 1.7 Hz, $CH_2CCH{=}C\underline{H}O$), 7.42 (1H, s, $CH_2C{=}C\underline{H}O$); ^{13}C NMR (150 MHz; $CDCl_3$): δ 56.8 ($\underline{C}H_2OH$), 109.9 ($CH_2C\underline{C}H$), 125.2 ($CH_2\underline{C}CH$), 140.1 ($CH_2C{=}\underline{C}HO$), 143.6 ($CH_2CCH{=}\underline{C}HO$); *m/z* (EI): 98 ($M^+$, 81%), 81 ($M^+$–OH, 100); HRMS (EI): $C_5H_6O_2$ (M^+) requires: 98.0362; found 98.0365.

<u>165.</u> 3-(Bromomethyl)furan



164 **165**

[Method 1]

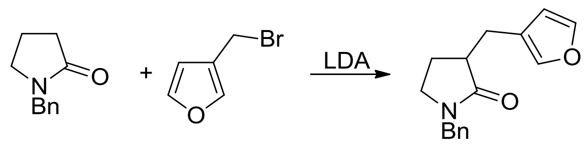
Prepared by the method of Wang.[147] A stirred solution of CBr_4 (1.4 g, 4.2 mmol) in CH_2Cl_2 (5 mL) at 0 ºC was treated with alcohol **164** (345 mg, 3.52 mmol) in CH_2Cl_2 (5 mL) followed portionwise by PPh_3 (1.48 g, 5.63 mmol) over 6 mins. The reaction mixture was stirred for 2 h then concentrated *in vacuo* to give a brown residue. The residue was washed with Et_2O (2 × 25 mL) and THF (2 × 5 mL). The washings were diluted with petroleum ether (75 mL) and filtered. The filtrate was concentrated *in vacuo* to give bromide **165** (85 mg, 15%) which was used without further purification: ^{1}H NMR (500

MHz; $CDCl_3$): δ 4.37 (2H, s, C<u>H</u>$_2$Br), 6.45 (1H, dd, *J* 1.9, 0.9 Hz CH_2CC<u>H</u>=CHO), 7.40 (1H, t, *J* 1.7 Hz CH_2CCH=C<u>H</u>O), 7.48 (1H, br sxt, *J* 0.8 Hz CH_2CCH=C<u>H</u>O).

[Method 2]

A stirred solution of alcohol **164** (0.87 mL, 10 mmol) in THF (10 mL) at −78 ºC was treated dropwise with PBr_3 (0.33 mL, 3.5 mmol) then stirred at 0 ºC for 2 h. The reaction mixture was diluted with saturated aq. $NaHCO_3$ solution (5 mL), H_2O (5 mL) and the organic material extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with H_2O (15 mL), brine (15 mL), dried ($MgSO_4$) then concentrated *in vacuo* to a volume of approximately 10 mL. The solution was stored over activated sieves (4 Å) under an atmosphere of argon at −18 ºC and used as a solution without further purification.

<u>167.</u> 1-Benzyl-3-(furan-3-ylmethyl)pyrrolidin-2-one

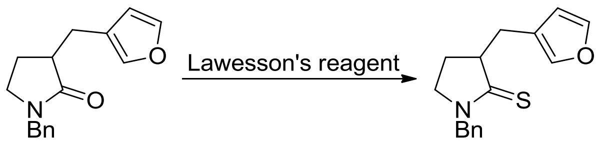


165 **167**

A stirred solution of diisopropylamine (65 µL, 0.63 mmol) in THF (6 mL) at –78 ºC was treated dropwise with *n*-butyllithium (2 M in hexanes, 0.33 mL, 0.65 mmol) then stirred for 20 mins. The solution was treated with *N*-benzylpyrrolidin-2-one (92 µL, 0.57 mmol) in THF (3 mL), stirred for 1 h then treated with bromide **165** (84 mg, 0.52 mmol) in THF (3 mL). The reaction mixture was stirred for 1 h, quenched with saturated aq. NH_4Cl solution (7 mL) then warmed to room temperature. The mixture was diluted with H_2O (10 mL) and the organic material extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 15-20% EtOAc in petroleum ether) gave lactam **167** (28 mg, 21%) as an oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2921 (C-H), 2872 (C-H), 1678 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.70 (1H, dq, *J* 12.9, 8.5 Hz, 1 of C<u>H</u>$_2$CH$_2$N), 2.04-2.14 (1H, m, 1 of C<u>H</u>$_2$CH$_2$N), 2.65 (1H, dd, *J* 13.9, 8.3 Hz, 1 of C<u>H</u>$_2$Fur), 2.71 (1H, dq, *J* 8.7, 3.8 Hz, C<u>H</u>C=O), 2.95 (1H, dd, *J* 14.3, 3.8 Hz, 1 of C<u>H</u>$_2$Fur), 3.07 (1H, dt, *J* 9.4, 3.4 Hz, 1 of C<u>H</u>$_2$NBn), 3.14 (1H, dt, *J* 9.8, 7.9 Hz, 1 of C<u>H</u>$_2$NBn), 4.41 (1H, d, *J* 14.7 Hz, 1 of C<u>H</u>$_2$Ph), 4.48 (1H, d, *J* 14.7 Hz, 1 of C<u>H</u>$_2$Ph), 6.29

(1H, d, *J* 0.9 Hz, $CH_2CC\underline{H}$), 7.16-7.21 (2H, m, aromatic C$\underline{H}$), 7.27-7.35 (5H, m, aromatic C$\underline{H}$, CCH=C$\underline{H}$O, CH_2C=C$\underline{H}$O); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.9 ($\underline{C}H_2CH_2N$), 26.2 ($\underline{C}H_2$Fur), 42.6 ($\underline{C}$HC=O), 44.9 ($\underline{C}H_2$NBn), 46.9 ($\underline{C}H_2$Ph), 111.5 ($\underline{C}$H=CHO), 121.9 ($\underline{C}$CH=CHO), 127.6 (aromatic $\underline{C}$), 128.2 (aromatic $\underline{C}$H), 128.8 (aromatic $\underline{C}$H), 136.5 (aromatic $\underline{C}$H), 140.0 (CH=$\underline{C}$HO), 143.0 (C=$\underline{C}$HO), 175.9 ($\underline{C}$=O); *m/z* (EI): 255 (M^+, 100%); HRMS (EI): $C_{16}H_{17}NO_2$ (M^+) requires: 255.1254; found 255.1263.

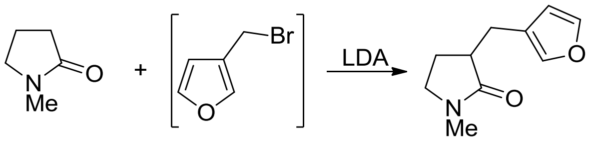
<u>168.</u> 1-Benzyl-3-(furan-3-ylmethyl)pyrrolidine-2-thione



167 **168**

A stirred solution of lactam **167** (28 mg, 0.11 mmol) in THF (5 mL) was treated with Lawesson's reagent (27 mg, 0.066 mmol) and heated to 40 ºC for 135 mins. The reaction mixture was treated with further Lawesson's reagent (20 mg, 0.049 mmol) and heated to reflux for 1 h. The reaction mixture was treated with H_2O (5 mL) and the organic material extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 15% EtOAc in petroleum ether) gave thiolactam **168** (18 mg, 60%) as a colourless oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2942 (C-H), 2918 (C-H), 2875 (C-H), 1504 (C=S); ^{1}H NMR (600 MHz, CDCl3) δ 1.70-1.79 (1H, m, 1 of $C\underline{H}_2CH_2N$), 2.15 (1H, dtd, *J* 12.9, 8.6, 4.5 Hz, 1 of $C\underline{H}_2CH_2N$), 2.78 (1H, dd, *J* 14.3, 8.7 Hz, 1 of $C\underline{H}_2$Fur), 3.11-3.19 (1H, m, C$\underline{H}$C=S), 3.22 (1H, dd, *J* 14.3, 4.1 Hz, 1 of $C\underline{H}_2$Fur), 3.34 (1H, ddd, *J* 11.2, 8.9, 4.7 Hz, 1 of $C\underline{H}_2$NBn), 3.42 (1H, dt, *J* 11.3, 7.9 Hz, 1 of $C\underline{H}_2$NBn), 4.94 (1H, d, *J* 14.3 Hz, 1 of $C\underline{H}_2$Ph), 5.03 (1H, d, *J* 14.3 Hz, 1 of $C\underline{H}_2$Ph), 6.31 (1H, s, $CH_2CC\underline{H}$), 7.23-7.36 (7H, m, aromatic C$\underline{H}$, CCH=C$\underline{H}$O and CH_2C=C$\underline{H}$O); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.2 ($\underline{C}H_2CH_2N$), 29.3 ($\underline{C}H_2$Fur), 52.0 ($\underline{C}H_2$Ph), 52.3 ($\underline{C}H_2$NBn), 54.5 ($\underline{C}$HC=S), 111.5 ($\underline{C}$H=CHO), 121.7 ($\underline{C}$CH=CHO), 128.1 (aromatic $\underline{C}$), 128.4 (aromatic $\underline{C}$H), 128.9 (aromatic $\underline{C}$H), 135.1 (aromatic $\underline{C}$H), 140.1 (CH=$\underline{C}$HO), 143.0 (C=$\underline{C}$HO), 204.4 ($\underline{C}$=S); *m/z* (EI): 272 (MH^+, 100%); HRMS (EI): $C_{16}H_{18}NOS$ (M^+) requires: 272.1109; found 272.1108.

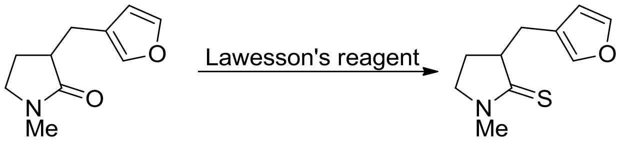
<u>170.</u> 3-(Furan-3-ylmethyl)-1-methylpyrrolidin-2-one



165 **170**

A stirred solution of diisopropylamine (1.25 mL, 12.1 mmol) in THF (30 mL) at –78 ºC was treated dropwise with *n*-butyllithium (2.5 M in hexanes, 4.4 mL, 11 mmol) and stirred for 20 mins. The reaction mixture was treated with *N*-benzylpyrrolidin-2-one (1.2 mL, 12 mmol) in THF (20 mL) and stirred for 1 h, then treated with a crude solution of bromide **165** (prepared from 10 mmol of alcohol **164**, using PBr_3) and stirred for 30 mins. The reaction mixture was quenched with saturated aq. NH_4Cl solution (20 mL) then warmed to room temperature. The mixture was diluted with H_2O (20 mL) and the organic material extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2; 20-50% EtOAc in petroleum ether) gave lactam **170** (710 mg, 40% over 2 steps from alcohol **164**) as a pale yellow oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2923 (C-H), 2873 (C-H), 1677 (C=O); ^{1}H NMR (500 MHz; $CDCl_3$): δ 1.68-1.76 (1H, m, 1 of C<u>H</u>$_2$CH$_2$N), 1.09-2.15 (1H, m, 1 of C<u>H</u>$_2$CH$_2$N), 2.57-2.66 (2H, m, 1 of C<u>H</u>$_2$Fur and C<u>H</u>C=O), 2.87 (3H, s, NC<u>H</u>$_3$), 2.92 (1H, dd, *J* 14.0, 2.9 Hz, 1 of C<u>H</u>$_2$Fur), 3.16 (1H, dt, *J* 9.1, 3.5 Hz 1 of C<u>H</u>$_2$NMe), 3.25 (1H, dt, *J* 9.6, 7.8 Hz, 1 of C<u>H</u>$_2$NMe), 6.27 (1H, dd, *J* 1.9, 0.9 Hz, CH$_2$CC<u>H</u>), 7.25 (1H, sxt, *J* 0.8 Hz, CH$_2$C=C<u>H</u>O), 7.34 (1H, t, *J* 1.7 Hz, CCH=C<u>H</u>O); ^{13}C NMR (125 MHz; $CDCl_3$): δ 24.0 (<u>C</u>H$_2$CH$_2$N), 26.4 (<u>C</u>H$_2$CH=CHO), 29.8 (<u>C</u>H$_3$N), 42.3 (<u>C</u>HC=ONCH$_3$), 47.6 (<u>C</u>H$_2$NMe), 111.4 (<u>C</u>H=CHO), 122.0 (<u>C</u>CH=CHO), 139.9 (CH=<u>C</u>HO), 143.0 (C=<u>C</u>HO), 175.9 (<u>C</u>=O); *m/z* (EI): 179 (M^+, 100%); HRMS (EI): $C_{10}H_{13}NO_2$ (M^+) requires: 179.0941; found 179.0944.

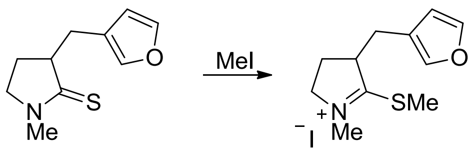
<u>171.</u> 3-(Furan-3-ylmethyl)-1-methylpyrrolidine-2-thione



170 **171**

A stirred solution of lactam **170** (690 mg, 3.96 mmol) in THF (20 mL) was treated with Lawesson's reagent (1.28 g 3.17 mmol). The mixture was heated to reflux for 5 h, then cooled to room temperature, diluted with H_2O (20 mL) and the organic material extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with H_2O (15 mL), brine (15 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 20% EtOAc in petroleum ether) gave thiolactam **171** (640 mg, 83%) as a yellow viscous oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2928 (C-H), 2875 (C-H), 1524 (C=S); ^{1}H NMR (500 MHz; $CDCl_3$): δ 1.74-1.82 (1H, m, 1 of C<u>H</u>$_2$CH$_2$N), 2.16-2.30 (1H, m, 1 of C<u>H</u>$_2$CH$_2$N), 2.74 (1H, dd, *J* 13.9, 8.6 Hz, 1 of C<u>H</u>$_2$Fur), 3.07-3.12 (1H, m, C<u>H</u>C=S), 3.17 (1H, dd, *J* 14.2, 3.8 Hz, 1 of C<u>H</u>$_2$Fur), 3.25 (3H, s, NC<u>H</u>$_3$), 3.45 (1H, ddd, *J* 11.2, 9.0, 4.7, 1 of C<u>H</u>$_2$NMe), 3.56 (1H, dt, *J* 11.3, 8.1 Hz, 1 of C<u>H</u>$_2$NMe), 6.30 (1H, dd, *J* 1.8, 0.8 Hz, CC<u>H</u>=CHO), 7.27 (1H, s, C=C<u>H</u>O), 7.34 (1H, t, *J* 1.7 Hz, CH=C*H*O); ^{13}C NMR (125 MHz; $CDCl_3$): δ 25.3 (<u>C</u>H$_2$CH$_2$N), 29.4 (<u>C</u>H$_2$CH=CHO), 35.7 (<u>C</u>H$_3$N), 54.2 (<u>C</u>HC=S), 55.2 (<u>C</u>H$_2$NMe), 111.4 (<u>C</u>H=CHO), 121.7 (<u>C</u>CH=CHO), 140.0 (CH=<u>C</u>HO), 143.0 (C=<u>C</u>HO), 203.8 (<u>C</u>=S); *m/z* (EI): 195 (MH$^+$, 75%), 167 (23), 162 (M$^+$–S, 54), 134 (29), 114 (46), 81 (74), 53 (100); HRMS (EI): $C_{10}H_{13}NOS$ (M$^+$) requires: 195.0712; found 195.0713.

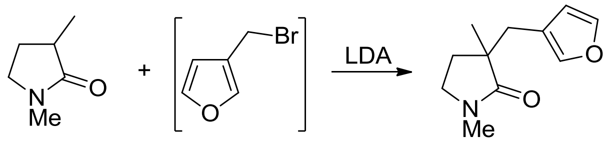
<u>176.</u> 4-(Furan-3-ylmethyl)-1-methyl-5-(methylthio)-3,4-dihydro-2*H*-pyrrol-1-ium iodide



171 **176**

A stirred solution of thiolactam **171** (640 mg, 3.28 mmol) in Et_2O (7 mL) was treated with MeI (1.22 mL, 19.7 mmol). The reaction mixture was heated to 60 ºC in a sealed tube for 16 h. The precipitate was collected by filtration and washed with Et_2O (20 mL), THF (20 mL) then dried under high vacuum to give *N*,*S*-ketene acetal **176** (943 mg, 85%) as a colourless solid: m.p. 115-116 ºC; ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2926 (C-H), 2855 (C-H), 1608; ^{1}H NMR (500 MHz; $CDCl_3$): δ 2.07 (1H, dddd, *J* 13.2, 8.0, 2.0, 1.7 Hz, 1 of $C\underline{H}_2CH_2N$), 2.85-2.97 (3H, m, $C\underline{H}_2$Fur and 1 of $C\underline{H}_2CH_2N$), 3.03 (3H, s, $SC\underline{H}_3$), 3.40 (3H, s, $NC\underline{H}_3$), 3.91-3.97 (1H, m, $C\underline{H}CSCH_3$), 4.10-4.15 (1H, m, 1 of $C\underline{H}_2NCH_3$), 4.25-4.29 (1H, m, 1 of $C\underline{H}_2NCH_3$), 6.30 (1H, dd, *J* 1.9, 1.0 Hz, $CH_2CC\underline{H}$), 7.40 (1H, t, *J* 1.7 Hz, $CH{=}C\underline{H}O$), 7.42 (1H, sxt, *J* 0.9 Hz, $C{=}C\underline{H}O$); ^{13}C NMR (125 MHz; $CDCl_3$): δ 17.2 ($\underline{C}H_3S$), 25.7 ($\underline{C}H_2CH_2N$), 27.6 ($\underline{C}H_2$Fur), 38.8 ($\underline{C}H_3N$), 52.0 ($\underline{C}HCSCH_3$), 62.2 ($\underline{C}H_2NCH_3$), 110.7 ($\underline{C}H{=}CHO$), 119.3 ($\underline{C}CH{=}CHO$), 140.9 ($CH{=}\underline{C}HO$), 144.0 ($C{=}\underline{C}HO$), 195.0 ($\underline{C}SNCH_3$); *m/z* (EI): 210 (M^+, 100%); HRMS (EI): $C_{11}H_{16}NOS$ (M^+) requires: 210.0947; found 210.0953.

<u>180.</u> 3-(Furan-3-ylmethyl)-1,3-dimethylpyrrolidin-2-one

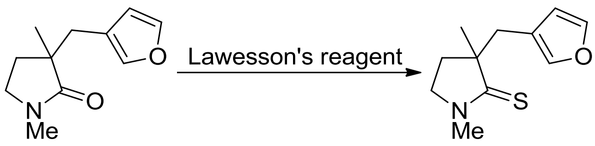


324 **165** **180**

A stirred solution of diisopropylamine (1.25 mL, 12.1 mmol) in THF (30 mL) at –78 ºC was treated dropwise with *n*-butyllithium (2.5 M in hexanes, 4.4 mL, 11 mmol) and stirred for 20 mins. The solution was treated with lactam **324** (1.37 g, 12.1 mmol) in THF (20 mL) and stirred for 1 h then treated with a crude solution of bromide **165** (prepared from 10.1 mmol of alcohol **164**, using PBr_3) and stirred for 30 mins. The reaction mixture was quenched with saturated aq. NH_4Cl solution (20 mL) then warmed to room temperature. The mixture was diluted with H_2O (20 mL) and the organic material extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2; 30-50% EtOAc in petroleum ether) gave lactam **180** (850 mg, 44% over 2 steps from alcohol **164**) as a yellow oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2962 (C-H), 2928 (C-H), 2872 (C-H), 1677 (C=O); ^{1}H NMR (500 MHz; $CDCl_3$): δ 1.18 (3H, s, $CC\underline{H}_3$), 1.73 (1H, ddd, *J* 13.9, 8.6, 5.3 Hz, 1 of $C\underline{H}_2CH_2N$), 2.00 (1H, ddd, *J* 12.8, 8.7, 5.5 Hz, 1 of $C\underline{H}_2CH_2N$), 2.46 (1H, d, *J* 14.2 Hz, 1 of $C\underline{H}_2$Fur), 2.74 (1H, d, *J* 14.2 Hz, 1 of $C\underline{H}_2$Fur), 2.78 (3H, s, $NC\underline{H}_3$), 2.87 (1H, ddd, *J* 9.5, 8.7, 5.5 Hz, 1 of $C\underline{H}_2NCH_3$), 3.16

(1H, ddd, 9.6, 8.7, 5.6 Hz, 1 of $C\underline{H}_2NCH_3$), 6.24 (1H, dd, *J* 1.9, 0.9 Hz, $CH_2CC\underline{H}$), 7.23 (1H, sxt, *J* 0.8 Hz, $C{=}C\underline{H}O$), 7.32 (1H, t, *J* 1.6 Hz, $CH{=}C\underline{H}O$); ^{13}C NMR (125 MHz; $CDCl_3$): δ 24.1 ($C\underline{C}H_3$), 29.9 ($N\underline{C}H_3$), 30.5 ($\underline{C}H_2CH_2N$), 33.5 ($\underline{C}H_2$Fur), 44.8 ($\underline{C}C{=}O$), 46.3 ($\underline{C}H_2NCH_3$), 112.1 ($\underline{C}H{=}CHO$), 120.8 ($\underline{C}CH{=}CHO$), 140.5 ($CH{=}\underline{C}HO$), 142.7 ($C{=}\underline{C}HO$), 178.5 ($\underline{C}{=}O$); *m/z* (CI): 194 (MH^+, 100%); HRMS (CI): $C_{11}H_{16}NO_2$ (MH^+) requires: 194.1181; found 194.1178.

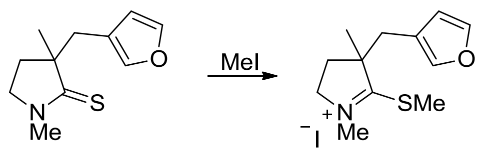
<u>181.</u> 3-(Furan-3-ylmethyl)-1,3-dimethylpyrrolidine-2-thione



180 **181**

A stirred solution of lactam **180** (850 mg, 4.40 mmol) in THF (20 mL) was treated with Lawesson’s reagent (1.42 g, 3.52 mmol). The mixture was heated to reflux for 5 h, then cooled to room temperature, diluted with H_2O (20 mL) and the organic material extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with H_2O (15 mL), brine (15 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 20% EtOAc in petroleum ether) gave thiolactam **181** (879 mg, 96%) as an oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2927 (C-H), 2875 (C-H), 1523 (C=S); ^1H NMR (500 MHz; $CDCl_3$): δ 1.30 (3H, s, $C C\underline{H}_3$), 1.85 (1H, ddd, *J* 12.7, 9.2, 6.7 Hz, 1 of $C\underline{H}_2CH_2N$), 2.11 (1H, ddd, *J* 13.5, 8.6, 4.9 Hz, 1 of $C\underline{H}_2CH_2N$), 2.58 (1H, d, *J* 14.4 Hz, 1 of $C\underline{H}_2$Fur), 2.89 (1H, d, *J* 14.4 Hz, 1 of $C\underline{H}_2$Fur), 3.10 (1H, ddd, *J* 11.1, 8.7, 6.7 Hz, 1 of $C\underline{H}_2NCH_3$), 3.17 (3H, s, $NC\underline{H}_3$), 3.43 (1H, ddd, *J* 11.2, 9.2, 5.1 Hz, 1 of $C\underline{H}_2NCH_3$), 6.28 (1H, dd, *J* 1.9, 0.9 Hz, $CH_2CC\underline{H}$), 7.26 (1H, sxt, *J* 0.8 Hz, $C{=}C\underline{H}O$), 7.31 (1H, t, *J* 1.6 Hz, $CH{=}C\underline{H}O$); ^{13}C NMR (125 MHz; $CDCl_3$): δ 27.5 ($C\underline{C}H_3$), 31.8 ($\underline{C}H_2CH_2N$), 35.8 ($N\underline{C}H_3$), 36.5 ($\underline{C}H_2$Fur), 53.9 ($\underline{C}H_2NCH_3$), 55.7 ($\underline{C}C{=}S$), 112.0 ($\underline{C}H{=}CHO$), 120.7 ($\underline{C}CH{=}CHO$), 140.6 ($CH{=}\underline{C}HO$), 142.6 ($C{=}\underline{C}HO$), 208.2 ($\underline{C}{=}S$); *m/z* (CI): 210 (MH^+, 100%); HRMS (CI): $C_{11}H_{15}NOS$ (MH^+) requires: 210.0953; found 210.0954.

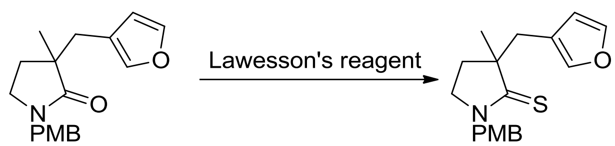
<u>182.</u> 4-(Furan-3-ylmethyl)-1,4-dimethyl-5-(methylsulfanyl)-3,4-dihydro-2*H*-pyrrol-1-ium iodide



181 **182**

A stirred solution of thiolactam **181** (879 mg, 4.20 mmol) in Et_2O (15 mL) was treated with MeI (1.56 mL, 25.2 mmol). The reaction mixture was heated to 60 ºC in a sealed tube over 3 days. The precipitate was collected by filtration and washed with THF (20 mL), then dried under high vacuum to give *N*,*S*-ketene acetal **182** (747 mg, 51%) as a colourless solid: m.p. 98-99 ºC; ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2949 (C-H), 1595, 1266, 727, 697; ^{1}H NMR (500 MHz; $CDCl_3$): δ 1.69 (3H, s, $CC\underline{H}_3$), 2.34 (2H, m, $C\underline{H}_2CH_2N$), 2.58 (1H, d, *J* 14.5 Hz, 1 of $C\underline{H}_2$Fur), 2.89 (1H, d, *J* 14.5 Hz, 1 of $C\underline{H}_2$Fur), 3.10 (3H, s, $SC\underline{H}_3$), 3.60 (3H, s, $NC\underline{H}_3$), 3.75 (1H, dt, *J* 12.6, 7.8 Hz, 1 of $C\underline{H}_2NCH_3$), 4.28 (1H, ddd, *J* 13.4, 8.8, 5.0 Hz, 1 of $C\underline{H}_2NCH_3$), 6.31 (1H, t, *J* 1.4 Hz, $CH_2CC\underline{H}$), 7.41 (1H, s, $C{=}C\underline{H}O$), 7.42 (1H, s, $CH{=}C\underline{H}O$); ^{13}C NMR (125 MHz; $CDCl_3$): δ 16.9 ($C\underline{C}H_3$) 25.6 ($\underline{C}H_3S$), 33.7 ($\underline{C}H_2CH_2N$), 35.0 ($\underline{C}H_2$Fur), 40.7 ($\underline{C}H_3N$), 59.7 ($\underline{C}CSCH_3$), 61.3 ($\underline{C}H_2NCH_3$), 111.4 ($\underline{C}H{=}CHO$), 118.2 ($\underline{C}CH{=}CHO$), 141.4 ($CH{=}\underline{C}HO$), 143.9 ($C{=}\underline{C}HO$), 193.8 ($\underline{C}SCH_3$); *m/z* (EI): 224 (M^+, 40%), 222 (41), 209 (M^+ $-CH_3$, 100); HRMS (EI): $C_{12}H_{18}NOS$ (M^+) requires: 224.1104; found 224.1111.

<u>188.</u> 3-(Furan-3-ylmethyl)-1-(4-methoxybenzyl)-3-methylpyrrolidine-2-thione

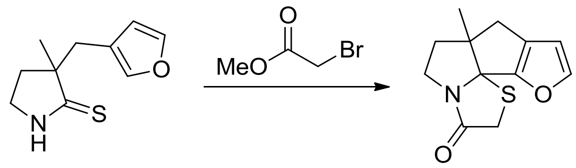


193 **188**

A stirred solution of lactam **193** (91 mg, 0.30 mmol) in toluene (5 mL) was treated with Lawesson’s reagent (68 mg, 0.17 mmol). The reaction mixture was heated to reflux for 6 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 15-30% EtOAc in hexane) gave thiolactam **188** (84 mg, 88%) as a yellow oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2962 (C-H), 2930 (C-H), 2876 (C-H), 1513 (C=S); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30

(3H, s, $CC\underline{H}_3$), 1.76 (1H, ddd, *J* 12.8, 8.7, 6.0 Hz, 1 of $C\underline{H}_2CH_2N$), 2.06 (1H, ddd, *J* 12.8, 8.7, 5.6 Hz, 1 of $C\underline{H}_2CH_2N$), 2.64 (1H, d, *J* 13.9 Hz, 1 of $C\underline{H}_2$Fur), 2.92 (1H, d, *J* 13.9 Hz, 1 of $C\underline{H}_2$Fur), 3.07 (1H, ddd, *J* 11.3, 8.7, 6.0 Hz, 1 of $C\underline{H}_2NCH_2Ar$), 3.30 (1H, ddd, *J* 11.1, 8.8, 5.6 Hz, 1 of $C\underline{H}_2NCH_2Ar$), 3.79 (3H, s, $C\underline{H}_3O$), 4.76 (1H, d, *J* 13.9 Hz, 1 of $NC\underline{H}_2Ar$), 4.96 (1H, d, *J* 13.9 Hz, 1 of $NC\underline{H}_2Ar$), 6.28 (1H, d, *J* 0.8 Hz, $CH_2CC\underline{H}$), 6.83 (2H, d, *J* 8.7 Hz, $CH_2CC\underline{H}{=}CH$), 7.17 (2H, d, *J* 8.7 Hz, $CH_2CCH{=}C\underline{H}$), 7.26 (1H, s, $C{=}C\underline{H}O$), 7.28 (1H, t, *J* 1.7 Hz, $CH{=}C\underline{H}O$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.3 ($C\underline{C}H_3$), 31.4 ($\underline{C}H_2CH_2N$), 36.0 ($\underline{C}H_2$Fur), 50.9 ($\underline{C}H_2NCH_2Ar$), 51.6 ($CH_2N\underline{C}H_2Ar$), 55.4 ($\underline{C}H_3O$), 55.9 ($\underline{C}C{=}S$), 112.3 ($\underline{C}H{=}CHO$), 114.2 ($CH_2C\underline{C}H{=}CH$), 120.6 ($\underline{C}CH{=}CHO$), 127.2 ($CH_2\underline{C}CH{=}CH$), 129.8 ($CH_2CCH{=}\underline{C}H$), 140.8 ($CH{=}\underline{C}HO$), 142.6 ($C{=}\underline{C}HO$), 159.4 ($CH_3O\underline{C}$), 208.5 ($\underline{C}{=}S$); *m/z* (EI): 315 (M^+, 36%), 234 (M^+–CH_2Fur, 71), 121 (PMB^+, 100); HRMS (EI): $C_{18}H_{21}NO_2S$ (M^+) requires: 315.1287; found 315.1295.

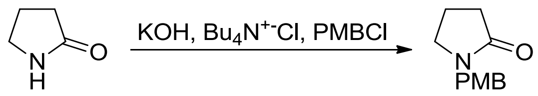
<u>191.</u> 6a-Methyl-5,6,6a,7-tetrahydrofuro[3'',2'':4',5']cyclopenta[1',2':2,3]pyrrolo[2,1-*b*]thiazol-3(2*H*)-one



198 **191**

A stirred solution of thiolactam **198** (21 mg, 0.11 mmol) in toluene (2 mL) was treated with methyl bromoacetate (12 µL, 0.13 mmol). The reaction mixture was heated to 150 ºC for 18 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 20% EtOAc in petroleum ether) gave tetracycle **191** (18 mg, 73%) as a yellow viscous oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2960 (C-H), 2922 (C-H), 2864 (C-H), 1683 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (3H, s, $CC\underline{H}_3$), 1.97 (1H, dt, *J* 13.0, 8.4 Hz, 1 of $C\underline{H}_2CH_2N$), 2.08 (1H, ddd, *J* 12.8, 7.9, 4.1 Hz, 1 of $C\underline{H}_2CH_2N$), 2.49 (1H, d, *J* 15.4 Hz, 1 of $C\underline{H}_2$Fur), 2.65 (1H, d, *J* 15.4 Hz, 1 of $C\underline{H}_2$Fur), 2.98 (1H, dtd, *J* 12.0, 8.1, 1.1 Hz, 1 of $C\underline{H}_2N$), 3.55 (1H, d, *J* 15.1 Hz, 1 of $C{=}OC\underline{H}_2$), 3.90 (1H, ddd, *J* 12.0, 8.3, 4.1 Hz, 1 of $C\underline{H}_2N$), 4.17 (1H, d, *J* 15.1 Hz, 1 of $C{=}OC\underline{H}_2$), 6.20 (1H, d, *J* 1.9 Hz, $C\underline{H}{=}CHO$), 7.44 (1H, d, *J* 1.9 Hz, $CH{=}C\underline{H}O$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.0 ($C\underline{H}_3$), 36.5 ($C{=}O\underline{C}H_2$), 37.0 ($\underline{C}H_2$Fur), 41.8 ($\underline{C}H_2CH_2N$), 42.7 ($\underline{C}H_2N$), 58.2 ($\underline{C}CH_3$), 80.3 ($N\underline{C}S$), 108.4 ($\underline{C}H{=}CHO$), 126.2 ($\underline{C}CH{=}CHO$), 148.7 ($CH{=}\underline{C}HO$), 155.6 ($C{=}\underline{C}O$), 171.0 ($\underline{C}{=}O$); *m/z* (EI): 235 (M^+, 75%), 220 (M^+–CH_3, 43), 175 (48), 162 (M^+–SCH_2CO, 72), 146 (100); HRMS (EI): $C_{12}H_{13}NO_2S$ (M^+) requires: 235.0662; found 235.0664.

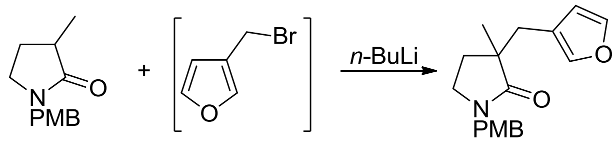
<u>192.</u> 1-(4-Methoxybenzyl)pyrrolidin-2-one



192

A suspension of freshly ground KOH (329 mg, 5.87 mmol) and tetra-*N*-butylammonium chloride (245 mg, 0.88 mmol) in THF (10 mL) was sonicated for 20 mins. The suspension was treated with pyrrolidin-2-one (0.45 mL, 5.9 mmol) and *p*-methoxybenzyl chloride (0.80 mL, 5.9 mmol) in THF (5 mL) and the reaction mixture was sonicated for 4 h then allowed to stand for 15 h at room temperature. The reaction mixture was treated with further KOH (66 mg, 1.2 mmol) and *p*-methoxybenzyl chloride (0.16 mL, 1.2 mmol) then sonicated for 1 h. The reaction mixture was filtered and washed with EtOAc (2 × 20 mL). The filtrate and washings were combined then concentrated *in vacuo*. The resulting residue was triturated with Et_2O, filtered, dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2; 50-100% EtOAc in petroleum ether) gave lactam **192** (941 mg, 79%), as a pale yellow oil which solidified upon storage at 4 ºC: m.p. 34-35 ºC; ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2926 (C-H), 2837 (C-H), 1668 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.96 (2H, quin, *J* 7.6 Hz, $C\underline{H}_2CH_2N$), 2.42 (2H, t, *J* 8.1 Hz, $C\underline{H}_2C{=}O$), 3.23 (2H, t, *J* 7.2 Hz, $C\underline{H}_2NCH_2Ar$), 3.79 (3H, s, $OC\underline{H}_3$), 4.38 (2H, s, $NC\underline{H}_2Ar$), 6.85 (2H, d, *J* 8.7 Hz, $CH_2CC\underline{H}{=}CH$), 7.16 (2H, d, *J* 8.7 Hz, $CH_2CCH{=}C\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.8 ($\underline{C}H_2CH_2N$), 31.2 ($\underline{C}H_2C{=}O$), 46.1 ($N\underline{C}H_2Ar$), 46.6 ($\underline{C}H_2NCH_2Ar$), 55.4 ($\underline{C}H_3O$), 114.1 ($CH_2C\underline{C}H{=}CH$), 128.8 ($CH_2\underline{C}CH{=}CH$), 129.6 ($CH_2CCH{=}\underline{C}H$), 159.1 ($CH_3O\underline{C}$), 175.0 ($\underline{C}{=}O$); *m/z* (CI): 206 (MH^+, 85%), 149 (15), 121 (93), 109 (50), 98 (90), 86 (100). HRMS (CI): $C_{11}H_{16}NO_2$ (MH^+) requires: 206.1181; found 206.1178.

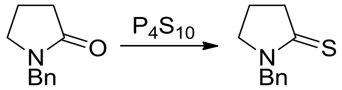
<u>193.</u> 3-(Furan-3-ylmethyl)-1-(4-methoxybenzyl)-3-methylpyrrolidin-2-one



325 **165** **193**

A stirred solution of lactam **325** (367 mg, 1.67 mmol) in THF (10 mL) at –78 ºC was treated with *n*-butyllithium (2.5 M in hexanes, 0.74 mL, 1.8 mmol) and stirred for 30 mins. The reaction mixture was treated with bromide **165** (prepared from 2.44 mmol of alcohol **164**, using PBr_3), stirred for 30 mins then warmed to room temperature. The reaction mixture was quenched with saturated aq. NH_4Cl solution (15 mL) and the organic material extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 30-50% EtOAc in hexane) gave lactam **193** (145 mg, 20% over 2 steps from alcohol **1**) as a yellow oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2963 (C-H), 2932 (C-H), 2872 (C-H), 1679 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (3H, s, $CC\underline{H}_3$), 1.66 (1H, ddd, *J* 12.8, 8.3, 4.9 Hz, 1 of $C\underline{H}_2CH_2N$), 1.97 (1H, ddd, *J* 12.8, 8.8, 6.6 Hz, 1 of $C\underline{H}_2CH_2N$), 2.49 (1H, d, *J*, 14.3 Hz, 1 of $C\underline{H}_2$Fur), 2.78 (1H, d, *J*, 14.3 Hz, 1 of $C\underline{H}_2$Fur), 2.84 (1H, td, *J* 9.2, 4.9 Hz, 1 of $C\underline{H}_2NCH_2Ar$), 3.04 (1H, ddd, *J* 9.6, 8.5, 6.4 Hz, 1 of $C\underline{H}_2NCH_2Ar$), 3.79 (3H, s, $C\underline{H}_3O$), 4.29 (1H, d, *J* 14.3 Hz, 1 of $NC\underline{H}_2Ar$), 4.37 (1H, d, *J* 14.3 Hz, 1 of $NC\underline{H}_2Ar$), 6.25 (1H, d, *J* 0.8 Hz, $CH_2CC\underline{H}$), 6.82 (2H, d, *J* 8.7 Hz, $CH_2CC\underline{H}$=CH), 7.07 (2H, d, *J* 8.7 Hz, $CH_2CCH=C\underline{H}$), 7.24 (1H, s, $C=C\underline{H}O$), 7.31 (1H, t, *J* 1.7 Hz, $CH=C\underline{H}O$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.0 ($C\underline{C}H_3$), 30.2 ($\underline{C}H_2CH_2N$), 33.1 ($\underline{C}H_2$Fur), 43.3 ($\underline{C}H_2NCH_2Ar$), 45.1 ($\underline{C}C=O$), 46.3 ($CH_2N\underline{C}H_2Ar$), 55.4 ($\underline{C}H_3O$), 112.3 ($\underline{C}H=CHO$), 114.0 ($CH_2C\underline{C}H=CH$), 120.8 ($\underline{C}CH=CHO$), 128.7 ($CH_2\underline{C}CH=CH$), 129.5 ($CH_2CCH=\underline{C}H$), 140.7 ($CH=\underline{C}HO$), 142.7 ($C=\underline{C}HO$), 159.1 ($CH_3O\underline{C}$), 178.4 ($\underline{C}$=O); *m/z* (EI): 299 (M^+, 37%), 217 (100), 121 (PMB^+, 66); HRMS (EI): $C_{18}H_{21}NO_3$ (M^+) requires: 299.1516; found 219.1509.

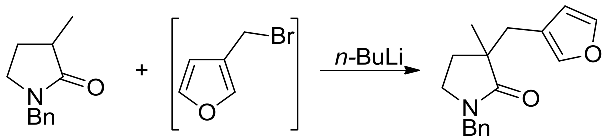
<u>194.</u> 1-Benzylpyrrolidine-2-thione[148]



194

A stirred solution of *N*-benzylpyrrolidin-2-one (1.04 g, 5.93 mmol) in toluene (12 mL) was treated with P_4S_{10} (2.60 g, 5.93 mmol) and heated to reflux for 4 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 40% Et_2O in hexane) gave thiolactam **194** (976 mg, 86%) as a colourless oil which solidified upon storage at 4 ºC: m.p. 70-71 ºC [lit.[148] = 70.2-71.8 ºC]; ν_{max}/cm^{-1} ($CDCl_3$ cast): 2962 (C-H), 2916 (C-H), 2874 (C-H), 1505 (C=S); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.01 (2H, quin, *J* 7.6 Hz, C<u>H</u>$_2$CH$_2$N), 3.10 (2H, t, *J* 7.9 Hz, C<u>H</u>$_2$C=S), 3.58 (2H, t, *J* 7.3 Hz, CH$_2$C<u>H</u>$_2$N), 4.99 (2H, s, C<u>H</u>$_2$Bn), 7.28-7.36 (5H, m, aromatic C<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.5 (<u>C</u>H$_2$CH$_2$N), 45.0 (CH$_2$<u>C</u>H$_2$N), 51.7 (<u>C</u>H$_2$Bn), 54.1 (<u>C</u>H$_2$C=S), 128.2 (aromatic <u>C</u>), 128.4 (aromatic <u>C</u>H), 129.0 (aromatic <u>C</u>H), 135.2 (aromatic <u>C</u>H), 201.9 (<u>C</u>=S).

<u>196.</u> 1-Benzyl-3-(furan-3-ylmethyl)-3-methylpyrrolidin-2-one

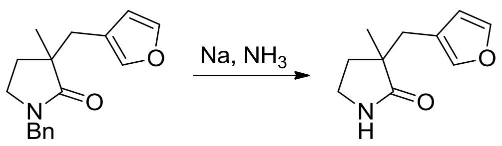


326 **165** **196**

A stirred solution of lactam **326** (1.56 g, 8.23 mmol) in THF (28 mL) at –78 ºC was treated dropwise with *n*-butyllithium (2.5 M in hexanes, 3.5 mL, 8.63 mmol) and stirred for 40 mins. The reaction mixture was treated with a solution of bromide **165** (prepared from 6.43 mmol of alcohol **164**, using PBr_3) and stirred for 30 mins and then warmed to room temperature. The reaction mixture was quenched with saturated aq. NH_4Cl solution (20 mL) and the organic material extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 25% EtOAc in petroleum ether) gave lactam **196** (480 mg, 28% over 2 steps from alcohol **164**) as an oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2961 (C-H), 2930 (C-H), 2871 (C-H), 1682 (C=O); ^{1}H NMR

(600 MHz, $CDCl_3$) δ 1.21 (3H, s, CC<u>H</u>$_3$), 1.68 (1H, ddd, *J* 12.8, 8.3, 4.5 Hz, 1 of C<u>H</u>$_2$CH$_2$N), 1.99 (1H, ddd, *J* 12.8, 9.0, 6.4 Hz, 1 of C<u>H</u>$_2$CH$_2$N), 2.50 (1H, d, *J*, 13.9 Hz, 1 of C<u>H</u>$_2$Fur), 2.80 (1H, d, *J*, 13.9 Hz, 1 of C<u>H</u>$_2$Fur), 2.86 (1H, td, *J* 9.0, 4.5 Hz, 1 of C<u>H</u>$_2$NBn), 3.06 (1H, ddd, *J* 9.7, 8.4, 6.4 Hz, 1 of C<u>H</u>$_2$NBn), 4.36 (1H, d, *J* 14.7 Hz, 1 of NC<u>H</u>$_2$Ph), 4.43 (1H, d, *J* 14.7 Hz, 1 of NC<u>H</u>$_2$Ph), 6.26 (1H, d, *J* 0.8 Hz, CH$_2$CC<u>H</u>), 7.11-7.33 (7H, m, aromatic C<u>H</u>, C=C<u>H</u>O, CH=C<u>H</u>O); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.0 (C<u>C</u>H$_3$), 30.2 (<u>C</u>H$_2$CH$_2$N), 33.2 (<u>C</u>H$_2$Fur), 43.4 (<u>C</u>C=O), 45.1 (<u>C</u>H$_2$NBn), 46.9 (<u>C</u>H$_2$Ph), 112.3 (<u>C</u>H=CHO), 120.7 (<u>C</u>CH=CHO), 127.6 (aromatic <u>C</u>), 128.1 (aromatic <u>C</u>H), 128.7 (aromatic <u>C</u>H), 136.6 (aromatic <u>C</u>H), 140.8 (CH=<u>C</u>HO), 142.7 (C=<u>C</u>HO), 178.5 (<u>C</u>=O); *m/z* (EI): 269 (M^+, 31%), 254 (M^+ –CH_3, 13), 187 (M^+ –CH$_2$Fur, 100), 158 (20), 91 ($PhCH_2^+$, 69); HRMS (EI): $C_{17}H_{19}NO_2$ (M^+) requires: 269.1410; found 269.1407.

<u>197.</u> 3-(Furan-3-ylmethyl)-3-methylpyrrolidin-2-one

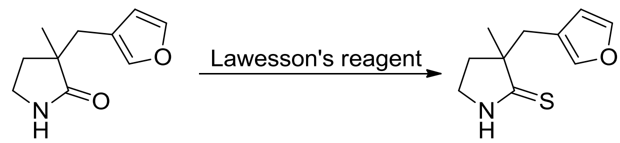


196 **197**

A solution of lactam **196** (373 mg, 1.38 mmol) in THF (15 mL) was added to liquid NH_3 (ca. 15 mL) at –78 ºC. The stirred solution was treated with Na (65 mg, 2.8 mmol) and stirred for 10 mins. The reaction mixture was quenched with saturated aq. NH_4Cl solution (15 mL) and the mixture was warmed to room temperature overnight. The solvent was removed *in vacuo* and the organic material extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with H_2O (30 mL), brine (30 mL) dried ($MgSO_4$) then concentrated *in vacuo* to give lactam **197** (234 mg, 95%) as a pale yellow oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 3230 (br, N-H), 2964 (C-H), 2927 (C-H), 2872 (C-H), 1692 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.17 (3H, s, CC<u>H</u>$_3$), 1.78 (1H, ddd, *J* 12.7, 8.0, 4.5 Hz, 1 of C<u>H</u>$_2$CH$_2$N), 2.09 (1H, ddd, *J* 12.7, 8.6, 6.6 Hz, 1 of C<u>H</u>$_2$CH$_2$N), 2.48 (1H, d, *J* 14.7 Hz, 1 of C<u>H</u>$_2$Fur), 2.71 (1H, d, *J* 14.7 Hz, 1 of C<u>H</u>$_2$Fur), 3.04 (1H, td, *J* 9.0, 4.5 Hz, 1 of C<u>H</u>$_2$N), 3.19-3.26 (1H, m, 1 of C<u>H</u>$_2$N), 6.28 (1H, s, CH$_2$CC<u>H</u>), 6.79 (1H, br s, N<u>H</u>), 7.24 (1H, s, CH=C<u>H</u>O), 7.32 (1H, s, C=C<u>H</u>O); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.5 (C<u>C</u>H$_3$), 32.7 (<u>C</u>H$_2$CH$_2$N), 32.8 (<u>C</u>H$_2$Fur), 39.0 (<u>C</u>C=O), 44.0 (<u>C</u>H$_2$N), 112.2 (<u>C</u>H=CHO), 120.7 (<u>C</u>CH=CHO), 140.7 (CH=<u>C</u>HO), 142.8 (C=<u>C</u>HO), 182.8 (<u>C</u>=O); *m/z* (EI): 179

(M^+, 41%), 164 (M^+ $-CH_3$, 35), 98 (35), 82 ($FurCH_2^+$, 100); HRMS (EI): $C_{10}H_{13}NO_2$ (M^+) requires: 179.0941; found 179.0944.

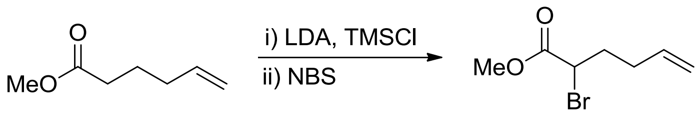
198. **3-(Furan-3-ylmethyl)-3-methylpyrrolidine-2-thione**



197 **198**

A stirred solution of lactam **197** (234 mg, 1.31 mmol) in THF (5 mL) was treated with Lawesson's reagent (292 mg, 0.721 mmol). The reaction mixture was heated to 60 ºC for 2 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 25% EtOAc in petroleum ether) gave thiolactam **198** (204 mg, 80%) as an orange oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 3166 (br, N-H), 2967 (C-H), 2926 (C-H), 2888 (C-H), 1524 (C=S); ^1H NMR (600 MHz, $CDCl_3$) δ 1.30 (3H, s, $C\underline{H}_3$), 1.95 (1H, ddd, *J* 12.8, 8.7, 5.6 Hz, 1 of $C\underline{H}_2CH_2N$), 2.23 (1H, ddd, *J* 12.9, 8.6, 6.0 Hz, 1 of $C\underline{H}_2CH_2N$), 2.67 (1H, d, *J* 13.9 Hz, 1 of $C\underline{H}_2Fur$), 2.88 (1H, d, *J* 13.9 Hz, 1 of $C\underline{H}_2Fur$), 3.16 (1H, dddd, *J* 14.3, 8.7, 5.6, 1.1 Hz, 1 of $C\underline{H}_2N$), 3.40 (1H, dddd, *J* 14.3, 8.7, 5.6, 1.1 Hz, 1 of $C\underline{H}_2N$), 6.37 (1H, d, *J* 0.9 Hz, $CH_2CC\underline{H}$), 7.31 (1H, s, $C{=}C\underline{H}O$), 7.33 (1H, t, *J* 1.7 Hz, $CH{=}C\underline{H}O$), 7.67 (1H, br s, $N\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.6 ($C\underline{C}H_3$), 33.6 ($\underline{C}H_2Fur$), 35.4 ($\underline{C}H_2CH_2N$), 45.7 ($\underline{C}H_2N$), 54.2 ($\underline{C}C{=}S$), 112.1 ($\underline{C}H{=}CHO$), 120.5 ($\underline{C}CH{=}CHO$), 140.7 ($CH{=}\underline{C}HO$), 142.7 ($C{=}\underline{C}HO$), 213.0 ($\underline{C}{=}S$); *m/z* (EI): 195 (M^+, 100), 180 (M^+ $-CH_3$, 45), 162 (16), 114 (22), 81 ($FurCH_2^+$, 60); HRMS (EI): $C_{10}H_{13}NOS$ (M^+) requires: 195.0712; found 195.0718.

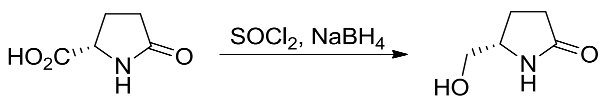
200. **Methyl 2-bromohex-5-enoate**



217 **200**

A stirred solution of diisopropylamine (0.315 mL, 2.26 mmol) in THF (3 mL) was cooled to 0 ºC and treated dropwise with *n*-butyllithium (2.5 M in hexanes, 0.904 mL, 2.26 mmol) and stirred for 15 mins then cooled to −78 ºC. A solution ester **217** (290 mg, 2.26 mmol) in THF (0.5 mL) was added and the mixture stirred for 15 mins. The reaction mixture was treated with TMSCl (0.43 mL, 3.39 mmol) and stirred for 1 h and then warmed room temperature. The mixture was concentrated *in vacuo* and diluted with pentane (5 mL), filtered then concentrated *in vacuo* to give a silyl enol ether which was dissolved in CH_2Cl_2 (2 mL). The solution was cooled to 0 ºC and treated with NBS (402 mg, 2.26 mmol). The reaction mixture was stirred for 5 h then washed with saturated aq. NH_4Cl solution (5 mL), brine (5 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petroleum ether) gave ester **200** (18 mg, 4%) as an oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2954 (C-H), 2919 (C-H), 2850 (C-H), 1743 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 2.05-2.28 (4H, m, $CHBrC\underline{H}_2$, $C\underline{H}_2CH=CH_2$), 3.78 (3H, s, $C\underline{H}_3O$), 4.24 (1H, dd, *J* 8.1, 6.2 Hz, $C=OC\underline{H}Br$), 5.04 (1H, d, *J* 10.2 Hz, $CH=C\underline{H}_2^{cis}$), 5.08 (1H, dd, *J* 17.3, 1.5 Hz, $CH=C\underline{H}_2^{trans}$), 5.75 (1H, ddt, *J* 17.3, 10.5, 6.4 Hz, $C\underline{H}=CH_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 31.3 ($CHBr\underline{C}H_2$), 33.9 ($C\underline{H}_2CH=CH_2$), 45.1 ($C=O\underline{C}HBr$), 53.1 ($\underline{C}H_3O$), 116.6 ($CH=\underline{C}H_2$), 136.1 ($\underline{C}H=CH_2$), 170.4 ($\underline{C}=O$); *m/z* (CI): 207/209 (MH^+, 62%), 175/177 (MH^+–HOMe, 16), 127 (MH^+–HBr, 100); HRMS (CI): $C_7H_{12}{}^{79}BrO_2$ (MH^+) requires: 207.0021; found 207.0019.

<u>203.</u> (*S*)-5-(Hydroxymethyl)pyrrolidin-2-one

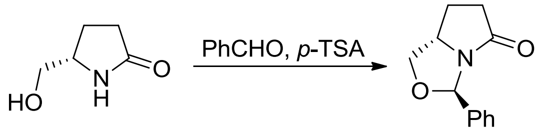


203

Prepared by the method of Tanner.[83] A stirred solution of (*S*)-pyroglutamic acid (14.2 g, 110 mmol) in MeOH (350 mL) at –15 ºC was treated dropwise with $SOCl_2$ (9.6 mL, 132 mmol) and stirred for 30 mins then warmed to room temperature over 1 h and stirred for an additional 1 h. The reaction mixture was concentrated *in vacuo* to give a colourless oil which was subsequently dissolved in EtOH (350 mL) then cooled to 0 ºC. The solution was treated portionwise (*ca*. 1 g portions) with $NaBH_4$ (8.32 g, 220 mmol) then warmed to room temperature overnight. The reaction mixture was treated with AcOH (15 mL, 262 mmol) and stirred for 30 mins then filtered through Celite®. SiO_2 was added to the filtrate, which was then concentrated *in vacuo*. The mixture was added to a short pad of SiO_2 and elution with 20% MeOH in EtOAc afforded lactam **203** (11.2 g, 88%) as a colourless solid: ν_{max}/cm^{-1} (solid): 3254 (br, O-H), 2928 (C-H), 2874 (C-H), 1676 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 1.80 (1H, dddd, *J* 13.0, 9.7, 7.2, 5.5 Hz, 1 of $C\underline{H}_2CH_2C=O$), 2.18 (1H, dddd, *J* 13.0, 9.5, 8.2, 6.6 Hz, 1 of $C\underline{H}_2CH_2C=O$), 2.28-2.43 (2H, m, $C\underline{H}_2C=O$), 3.47 (1H, dd, *J* 11.3, 7.2 Hz, 1 of $OC\underline{H}_2$), 3.60 (1H, br s, $O\underline{H}$), 3.69

(1H, dd, *J* 11.3, 3.0 Hz, 1 of OC<u>H</u>$_2$), 3.76-3.85 (1H, m, OCH_2C<u>H</u>), 6.99 (1H, br s, N<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.7 (<u>C</u>H_2CH_2C=O), 30.3 (<u>C</u>H_2C=O), 56.4 (OCH_2<u>C</u>H), 66.1 (O<u>C</u>H_2), 179.3 (<u>C</u>=O).

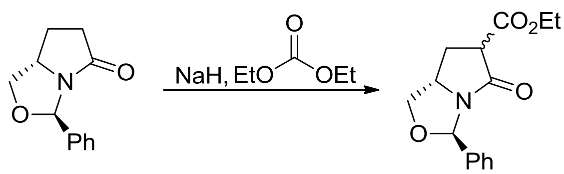
<u>204.</u> (3*R*,7a*S*)-3-Phenyltetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one



203 **204**

Prepared by the method of Thottathil.[84] To a stirred suspension of lactam **203** (9.2 g, 80 mmol) in toluene (54 mL) was added benzaldehyde (10.5 mL, 104 mmol) and *p*-TSA (152 mg, 0.80 mmol). The flask was fitted with a Dean-Stark trap and the suspension was heated to reflux for 4.5 h. The reaction mixture was washed with 5% $NaHCO_3$ solution (2 × 20 mL), saturated aq. $Na_2S_2O_5$ solution (4 × 20 mL), H_2O (20 mL), brine (20 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50% EtOAc in petroleum ether) gave lactam **204** (8.7 g, 54%) as a colourless oil: ν_{max}/cm^{-1} ($CHCl_3$ cast): 2977 (C-H), 2947 (C-H), 2881 (C-H), 1698 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.87-2.00 (1H, m, 1 of C<u>H</u>$_2CH_2$C=O), 2.38 (1H, dddd, *J* 17.3, 11.3, 7.5, 3.8 Hz, 1 of C<u>H</u>$_2CH_2$C=O), 2.56 (1H, ddd, *J* 17.3, 9.8, 3.8 Hz, 1 of C<u>H</u>$_2$C=O), 2.82 (1H, dt, *J* 17.1, 9.7 Hz, 1 of C<u>H</u>$_2$C=O), 3.49 (1H, t, *J* 8.1 Hz, 1 of OC<u>H</u>$_2$), 4.10-4.19 (1H, m, CH_2C<u>H</u>N), 4.23 (1H, dd, *J* 8.1, 6.2 Hz, 1 of OC<u>H</u>$_2$), 6.33 (1H, s, C<u>H</u>Ph), 7.28-7.48 (5H, m, aromatic C<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.2 (<u>C</u>H_2CH_2C=O), 33.6 (<u>C</u>H_2C=O), 58.9 (OCH_2<u>C</u>H), 71.8 (O<u>C</u>H_2), 87.2 (<u>C</u>HPh), 126.0 (aromatic <u>C</u>H), 128.6 (aromatic <u>C</u>H), 128.7 (aromatic <u>C</u>H), 138.9 (aromatic <u>C</u>), 178.2 (<u>C</u>=O).

<u>205.</u> (3*R*,7a*S*)-Ethyl 5-oxo-3-phenylhexahydropyrrolo[1,2-*c*]oxazole-6-carboxylate

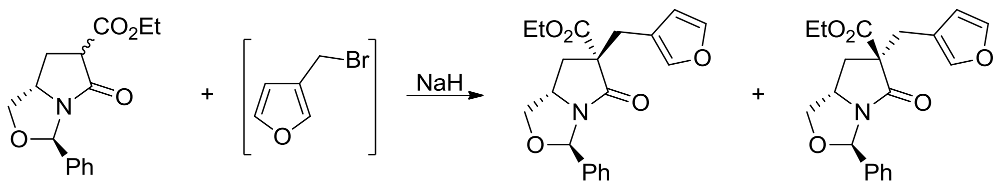


204 **205**

Prepared by the method of Moloney.[82] A flask containing a stirred solution of lactam **204** (8.7 g, 43 mmol) and diethyl carbonate (21 mL, 171 mmol) in toluene was fitted with a

Dean-Stark trap. The solution was heated to reflux for 4.5 h, cooled to 0 ºC then added to pre-washed NaH (60% dispersion in mineral oil, 4.12 g, 103 mmol). The reaction mixture was heated to reflux for 14 h then cooled to 0 ºC. The mixture was treated with AcOH (4.4 g, 73.3 mmol) then stirred for 1 h at room temperature. The mixture was filtered and the filtrate concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 30-40-50% EtOAc in petroleum ether) gave lactam **205** (7.3 g, 62%, 13:1 ratio of diastereoisomers) as a yellow solid: m.p. 66-67 ºC [lit.[82] 85-87 ºC, 1:1 ratio of diastereoisomers]; ν_{max}/cm^{-1} (solid): 2985 (C-H), 2917 (C-H), 2875 (C-H), 1736 (C=O, ester), 1687 (C=O, amide); ^{1}H NMR (600 MHz, $CDCl_3$, data for the major diastereoisomer only) δ 1.33 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 2.42 (1H, ddd, *J* 13.3, 9.9, 6.2 Hz, 1 of $C\underline{H}_2$CHC=O), 2.57 (1H, ddd, *J* 13.2, 9.0, 7.2 Hz, 1 of $C\underline{H}_2$CHC=O), 3.69 (1H, t, *J* 8.1 Hz, 1 of $OC\underline{H}_2$), 3.87 (1H, t, *J* 9.6 Hz, C$\underline{H}$C=O), 4.09-4.17 (1H, m, $OCH_2C\underline{H}$), 4.20-4.34 (3H, m, $C\underline{H}_2CH_3$, 1 of $OC\underline{H}_2$), 6.32 (1H, s, C$\underline{H}$Ph), 7.30-7.48 (5H, m, aromatic C$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$, data for the major diastereoisomer only) δ 14.3 ($CH_2\underline{C}H_3$), 27.6 ($\underline{C}H_2$CHC=O), 51.7 ($\underline{C}$HC=O), 57.0 ($OCH_2\underline{C}H$), 62.1 ($\underline{C}H_2CH_3$), 72.0 ($O\underline{C}H_2$), 87.2 ($\underline{C}$HPh), 126.0 (aromatic $\underline{C}$H), 128.6 (aromatic $\underline{C}$H), 128.8 (aromatic $\underline{C}$H), 138.4 (aromatic $\underline{C}$), 169.3 (N$\underline{C}$=O), 172.3 (CH$\underline{C}$=O).

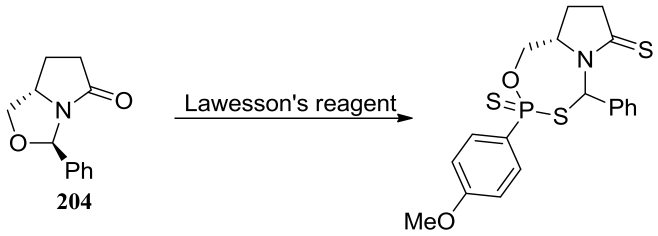
<u>206.</u> Ethyl (2*R*,5*S*,7*S*)-7-(furan-3-ylmethyl)-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane-7-carboxylate



205 **165** **206** **327**

NaH (60% dispersion in oil, 620 mg, 15.3 mmol) was washed with hexanes to remove the oil then suspended in THF (80 mL) and cooled to 0 ºC and treated with lactam **205** (3.52 g, 12.8 mmol) in THF (20 mL) then warmed to room temperature and stirred for 30 mins. The reaction mixture was treated with a solution of bromide **165** (prepared from 16.8 mmol of alcohol **1**, using PBr_3) and stirred for 21 h. The reaction mixture was quenched with saturated aq. NH_4Cl solution (120 mL) and the organic material extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 20% Et_2O in petroleum ether) gave ethyl (2*R*,5*S*,7*R*)-7-(furan-3-ylmethyl)-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane-7-carboxylate (epimer of **206**) (312 mg, 7%, minor isomer) as a colourless solid: m.p. 50-52 ºC; $[\alpha]_D^{20}$ = +164.7, (*c* 0.99, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$): 2981 (C-H), 2938 (C-H), 2876 (C-H), 1736 (C=O, ester), 1708 (C=O, amide); ^1H NMR (600 MHz, $CDCl_3$) δ 1.27 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 1.87 (1H, dd, *J* 13.2, 6.8 Hz, 1 of $C\underline{H}_2CC{=}O$), 2.78 (1H, dd, *J* 13.2, 6.8 Hz, 1 of $C\underline{H}_2CC{=}O$), 3.09 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 3.14 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 3.18 (1H, t, *J* 7.9 Hz, 1 of $OC\underline{H}_2$), 4.14 (1H, dd, *J* 8.3, 6.4 Hz, 1 of $OC\underline{H}_2$), 4.17-4.28 (3H, m, $OCH_2C\underline{H}$ and $C\underline{H}_2CH_3$), 6.25-6.28 (2H, m, $C\underline{H}Ph$ and $CH_2CC\underline{H}$), 7.27-7.43 (7H, m, aromatic $C\underline{H}$, $C{=}C\underline{H}O$, $CH{=}C\underline{H}O$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2 ($CH_2\underline{C}H_3$), 29.2 ($\underline{C}H_2$Fur), 33.8 ($\underline{C}H_2CC{=}O$), 56.3 ($OCH_2\underline{C}H$), 61.6 ($\underline{C}C{=}O$), 62.2 ($\underline{C}H_2CH_3$), 72.1 ($O\underline{C}H_2$), 87.0 ($\underline{C}HPh$), 111.9 ($\underline{C}H{=}CHO$), 119.6 ($\underline{C}CH{=}CHO$), 126.1 (aromatic $\underline{C}H$), 128.6 (aromatic $\underline{C}H$), 128.8 (aromatic $\underline{C}H$), 138.1 (aromatic $\underline{C}$), 141.2 ($CH{=}\underline{C}HO$), 143.3 ($C{=}\underline{C}HO$), 170.7 ($N\underline{C}{=}O$), 173.0 ($C\underline{C}{=}O$); *m/z* (CI): 356 (MH^+, 100%); HRMS (CI): $C_{20}H_{22}NO_5$ (MH^+) requires: 356.1498; found 356.1504. Further elution (20% Et_2O in petroleum ether) afforded lactam **206** (1.86 g, 41%, major isomer) as a colourless oil: $[\alpha]_D^{20}$= +59.1, (*c* 0.81, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$): 2981 (C-H), 2939 (C-H), 2878 (C-H), 1740 (C=O, ester), 1704 (C=O, amide); ^1H NMR (600 MHz, $CDCl_3$) δ 1.32 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 2.32 (1H, dd, *J* 13.9, 7.9 Hz, 1 of $C\underline{H}_2CC{=}O$), 2.50 (1H, dd, *J* 13.9, 4.9 Hz, 1 of $C\underline{H}_2CC{=}O$), 3.07 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 3.12 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 3.62 (1H, dd, *J* 8.7, 7.9 Hz, 1 of $OC\underline{H}_2$), 3.70-3.78 (1H, m, $OCH_2C\underline{H}$), 4.19 (1H, dd, *J* 7.7, 6.2 Hz, 1 of $OC\underline{H}_2$), 4.22-4.32 (2H, m, $C\underline{H}_2CH_3$), 6.23 (1H, t, *J* 1.3 Hz, $CH_2CC\underline{H}$), 6.29 (1H, s, $C\underline{H}Ph$), 7.27-7.38 (7H, m, aromatic $C\underline{H}$, $C{=}C\underline{H}O$, $CH{=}C\underline{H}O$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2 ($CH_2\underline{C}H_3$), 29.8 ($\underline{C}H_2$Fur), 31.1 ($\underline{C}H_2CC{=}O$), 56.3 ($OCH_2\underline{C}H$), 60.7 ($\underline{C}C{=}O$), 62.2 ($\underline{C}H_2CH_3$), 71.7 ($O\underline{C}H_2$), 87.3 ($\underline{C}HPh$), 112.0 ($\underline{C}H{=}CHO$), 119.2 ($\underline{C}CH{=}CHO$), 126.0 (aromatic $\underline{C}H$), 128.5 (aromatic $\underline{C}H$), 128.8 (aromatic $\underline{C}H$), 138.4 (aromatic $\underline{C}$), 141.2 ($CH{=}\underline{C}HO$), 143.1 ($C{=}\underline{C}HO$), 171.2 ($N\underline{C}{=}O$), 174.9 ($C\underline{C}{=}O$); *m/z* (CI): 356 (MH^+, 100%); HRMS (CI): $C_{20}H_{22}NO_5$ (MH^+) requires: 356.1498; found 356.1507.

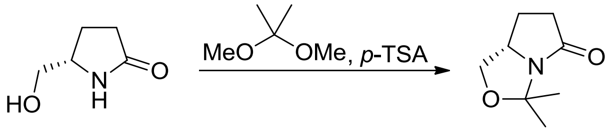
<u>207.</u> **(9a*S*)-3-(4-Methoxyphenyl)-5-phenyltetrahydropyrrolo[1,2-*e*][1,3,5,2]oxathiazaphosphepine-7(5*H*)-thione-3-sulfide**



204 **207**

A stirred solution of lactam **204** (207 mg, 1.02 mmol) in THF (5 mL) was treated with Lawesson's reagent (247 mg, 0.611 mmol) and heated to reflux for 6 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50% EtOAc in petroleum ether) gave thiolactam **207** (340 mg, 79%) as a colourless solid: m.p. 138-139 ºC; $[\alpha]_D^{20}$ = –74.0 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (solid): 2924 (C-H), 2838 (C-H), 1591 (C=S); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.97-2.08 (1H, m, 1 of $C\underline{H}_2CH_2C{=}O$), 2.35-2.46 (1H, m, 1 of $C\underline{H}_2CH_2C{=}O$), 3.12 (1H, ddd, *J* 18.1, 8.7, 2.6 Hz, 1 of $C\underline{H}_2C{=}S$), 3.21 (1H, ddd, *J* 17.3, 10.5, 8.3 Hz, 1 of $C\underline{H}_2C{=}S$), 3.89 (3H, s, $C\underline{H}_3O$), 4.04 (1H, ddd, *J* 28.2, 12.4, 5.6 Hz, 1 of $OC\underline{H}_2$), 4.91-4.97 (1H, m, $OCH_2C\underline{H}$), 5.09 (1H, ddd, *J* 15.2, 12.1, 6.2 Hz, 1 of $OC\underline{H}_2$), 6.99-7.07 (3H, m, $C\underline{H}Ph$ and 2 × $CH_3OC{=}CHC\underline{H}$), 7.28-7.39 (5H, m, aromatic $C\underline{H}$), 7.93 (2H, dd, *J* 13.9, 8.7 Hz, 2 × $CH_3OC{=}C\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.0 ($\underline{C}H_2CH_2C{=}O$), 43.7 ($C\underline{H}_2C{=}S$), 55.7 ($\underline{C}H_3O$), 62.5 ($OCH_2\underline{C}H$), 64.8 (d, J_{CP} 4.2 Hz, $\underline{C}HPh$), 65.6 (d, J_{CP} 6.6 Hz, $O\underline{C}H_2$), 114.5 (d, J_{CP} 16.1 Hz, $CH_3OC{=}CH\underline{C}H$), 124.7 (d, J_{CP} 129.9 Hz, $CH{=}\underline{C}P$), 127.3 (aromatic $C\underline{H}$), 129.11 (aromatic $C\underline{H}$), 129.15 (aromatic $C\underline{H}$), 133.5 (d, J_{CP} 14.3 Hz, $CH_3OC{=}\underline{C}H$), 135.4 (d, J_{CP} 6.6 Hz, aromatic $\underline{C}$), 163.6 (d, J_{CP} 3.6 Hz, $CH_3O\underline{C}$), 203.3 ($\underline{C}{=}S$); *m/z* (CI): 422 (MH^+, 44%), 300 (MH^+ –SCHPh, 100); HRMS (CI): $C_{20}H_{22}NO_2PS_3$ (MH^+) requires: 422.0472; found 422.0474.

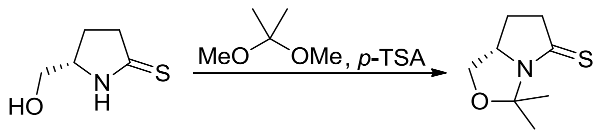
211. (*S*)-3,3-Dimethyltetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one[18]



203 **211**

A stirred suspension of lactam **203** (10.9 g, 94.7 mmol) in toluene (100 mL) was treated with 2,2-dimethoxypropane (15.1 mL, 123 mmol) and *p*-TSA (360 mg, 1.89 mmol) then heated to reflux for 2 h. MeOH was removed from the reaction mixture *via* distillation and further 2,2-dimethoxypropane (15.1 mL, 123 mmol) was added. The reaction was heated to reflux for 30 mins then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50-75% Et_2O in hexane) gave acetonide **211** (10.6 g, 72%) as a colourless solid: m.p. 24-25 ºC [lit.[18] = 36-37 ºC]; ν_{max}/cm^{-1} (solid): 2980 (C-H), 2933 (C-H), 2888 (C-H), 1670 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 1.45 (3H, s, C<u>H</u>$_3$), 1.65 (3H, s, C<u>H</u>$_3$), 1.75 (1H, tt, *J* 12.2, 9.0 Hz, 1 of C<u>H</u>$_2$CH$_2$C=O), 2.11-2.21 (1H, m, 1 of C<u>H</u>$_2$CH$_2$C=O), 2.53 (1H, dd, *J* 16.6, 9.0 Hz, 1 of C<u>H</u>$_2$C=O), 2.79 (1H, ddd, *J* 16.6, 12.0, 8.7 Hz, 1 of C<u>H</u>$_2$C=O), 3.44 (1H, t, *J* 8.8 Hz, 1 of OC<u>H</u>$_2$), 4.07 (1H, dd, *J* 8.3, 5.6 Hz, 1 of OC<u>H</u>$_2$), 4.25 (1H, tt, *J* 8.8, 6.0 Hz, CH$_2$C<u>H</u>N); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.9 (<u>C</u>H$_3$), 24.4 (<u>C</u>H$_2$CH$_2$C=O), 26.9 (<u>C</u>H$_3$), 37.3 (<u>C</u>H$_2$C=O), 61.7 (CH$_2$<u>C</u>HN), 70.0 (O<u>C</u>H$_2$), 91.4 (<u>C</u>(CH$_3$)$_2$), 171.6 (<u>C</u>=O).

212. (*S*)-3,3-Dimethyltetrahydropyrrolo[1,2-*c*]oxazole-5(3*H*)-thione

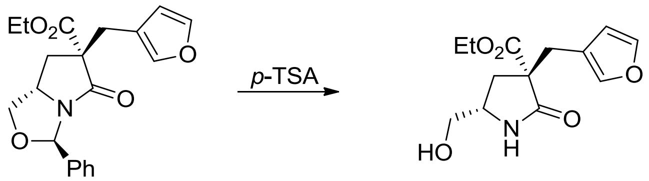


287 **212**

A stirred suspension of alcohol **287** (0.4 g, 3.1 mmol) in toluene (4 mL) was treated with 2,2-dimethoxypropane (0.487 mL, 3.96 mmol) and *p*-TSA (12 mg, 0.061 mmol). The mixture was heated to reflux for 3 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 30-50% Et_2O in petroleum ether) gave alcohol **212** (268 mg, 51%) as a colourless solid: m.p. 74-75 ºC; $[\alpha]_D^{20}$ = +241 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ cast): 2987 (C-H), 2940 (C-H), 2871 (C-H), 1476 (C=S); ^1H NMR (600 MHz, $CDCl_3$) δ 1.67 (3H, s, C<u>H</u>$_3$), 1.75-1.87 (4H, m, C<u>H</u>$_3$ and 1 of C<u>H</u>$_2$CH$_2$C=S), 2.17 (1H, dt, *J* 12.2, 6.3

Hz, 1 of C$\underline{H}_2$CH$_2$C=S), 3.25 (1H, dd, *J* 17.7, 8.3 Hz, 1 of C$\underline{H}_2$C=S), 3.34 (1H, ddd, *J* 17.3, 12.8, 7.2 Hz, 1 of C$\underline{H}_2$C=S), 3.53 (1H, dd, *J* 10.0, 8.5 Hz, 1 of OC$\underline{H}_2$), 4.10 (1H, dd, *J* 8.5, 5.5 Hz, 1 of OC$\underline{H}_2$), 4.49 (1H, tt, *J* 10.5, 5.5 Hz, CH$_2$C$\underline{H}$N); ^{13}C NMR (150 MHz, CDCl$_3$) δ 22.2 ($\underline{C}$H$_3$), 24.9 ($\underline{C}$H$_3$), 26.1 ($\underline{C}$H$_2$CH$_2$C=S), 52.5 ($\underline{C}$H$_2$C=S), 68.0 (O$\underline{C}$H$_2$), 69.6 (CH$_2\underline{C}$HN), 93.4 ($\underline{C}$(CH$_3$)$_2$), 195.8 ($\underline{C}$=S); *m/z* (CI): 172 (MH$^+$, 100%); HRMS (CI): $C_8H_{14}NOS$ (MH$^+$) requires: 172.0796; found 172.0791; anal. calcd for $C_8H_{14}NOS$: C, 56.10; H, 7.65; N, 8.18. Found: C, 56.22; H, 7.71; N, 8.16.

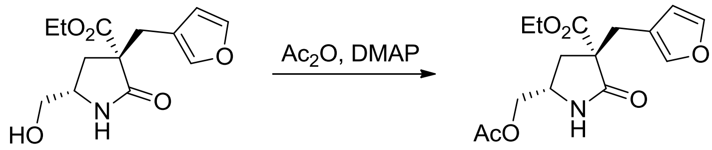
<u>213.</u> (3*S*,5*S*)-Ethyl 3-(furan-3-ylmethyl)-5-(hydroxymethyl)-2-oxopyrrolidine-3-carboxylate



206 **213**

A stirred solution of lactam **206** (557 mg, 1.57 mmol) in CH$_2$Cl$_2$ (42 mL) was treated with *p*-TSA (298 mg, 1.57 mmol) and stirred for 105 mins. The reaction mixture was passed through a short pad of silica gel, eluting with EtOAc to give lactam **213** (371 mg, 87%) as a colourless solid: m.p. 82-83 ºC; $[\alpha]_D^{20}$ = +6.45 (*c* 0.31, CHCl$_3$); ν_{max}/cm^{-1} (solid): 3227 (br, N-H) 2930 (C-H), 1721 (C=O, ester), 1676 (C=O, amide); ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.29 (3H, t, *J* 7.2 Hz, CH$_2$C$\underline{H}_3$), 2.24 (1H, dd, *J* 13.9, 8.7 Hz, 1 of C$\underline{H}_2$CC=O), 2.29 (1H, dd, *J* 13.6, 5.3 Hz, 1 of C$\underline{H}_2$CC=O), 2.43 (1H, br t, *J* 5.5 Hz, O$\underline{H}$), 3.02 (1H, d, *J* 14.3 Hz, 1 of C$\underline{H}_2$Fur), 3.08 (1H, d, *J* 14.3 Hz, 1 of C$\underline{H}_2$Fur), 3.37-3.44 (1H, br m, OCH$_2$C$\underline{H}$), 3.52 (1H, ddd, *J* 11.1, 7.0, 6.0 Hz, 1 of OC$\underline{H}_2$), 3.64 (1H, ddd, *J* 10.9, 5.3, 3.8 Hz, 1 of OC$\underline{H}_2$), 4.19-4.27 (2H, m, C$\underline{H}_2$CH$_3$), 6.30 (1H, d, *J* 0.9 Hz, CH$_2$CC$\underline{H}$), 6.49 (1H, br s, N$\underline{H}$), 7.30 (1H, s, C=C$\underline{H}$O), 7.35 (1H, t, *J* 1.7 Hz, CH=C$\underline{H}$O); ^{13}C NMR (150 MHz, CDCl$_3$) δ 14.2 (CH$_2\underline{C}$H$_3$), 29.6 ($\underline{C}$H$_2$Fur), 31.3 ($\underline{C}$H$_2$CC=O), 53.1 (OCH$_2\underline{C}$H), 55.9 ($\underline{C}$C=O), 62.2 ($\underline{C}$H$_2$CH$_3$), 66.0 (O$\underline{C}$H$_2$), 111.9 ($\underline{C}$H=CHO), 119.2 ($\underline{C}$CH=CHO), 141.2 (CH=$\underline{C}$HO), 143.3 (C=$\underline{C}$HO), 172.1 (N$\underline{C}$=O), 175.2 (C$\underline{C}$=O); *m/z* (ES$^+$): 290 (MNa$^+$, 100%), 222 (MNa$^+$ –C$_4$H$_3$O, 50); HRMS (ES$^+$): $C_{13}H_{17}NO_5Na$ (MNa$^+$) requires: 290.1004; found 290.1012.

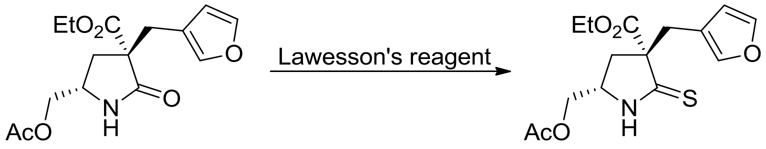
214. (3*S*,5*S*)-Ethyl 5-(acetoxymethyl)-3-(furan-3-ylmethyl)-2-oxopyrrolidine-3-carboxylate



213 **214**

A stirred solution of lactam **213** (269 mg, 1 mmol) in CH_2Cl_2 (10 mL) was treated with Ac_2O (105 µL, 1.1 mmol) and DMAP (24 mg, 0.2 mmol). The reaction mixture was allowed to stir for 80 mins then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 30-50% EtOAc in petroleum ether) gave lactam **214** (298 mg, 96%) as a colourless oil: $[\alpha]_D^{20} = -3.0$ (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film): 3114 (br, N-H), 2940 (C-H), 2912 (C-H), 2907 (C-H), 1734 (C=O, ester), 1697 (C=O, amide); ^1H NMR (600 MHz, $CDCl_3$) δ 1.30 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 2.06 (3H, s, $C\underline{H}_3C$=O), 2.28 (1H, dd, *J* 14.3, 8.7 Hz, 1 of $C\underline{H}_2CC$=O), 2.32 (1H, dd, *J* 13.9, 5.6 Hz, 1 of $C\underline{H}_2CC$=O), 3.02 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 3.09 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 3.43-3.51 (1H, m, $OCH_2C\underline{H}$), 3.93 (1H, dd, *J* 10.9, 8.7 Hz, 1 of $OC\underline{H}_2$), 4.16 (1H, dd, *J* 11.1, 4.0 Hz, 1 of $OC\underline{H}_2$), 4.24 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CH_3$), 6.06 (1H, br s, N$\underline{H}$), 6.30 (1H, d, *J* 0.9 Hz, $CH_2CC\underline{H}$), 7.30 (1H, s, C=C$\underline{H}$O), 7.35 (1H, t, *J* 1.7 Hz, CH=C$\underline{H}$O); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2 ($CH_2\underline{C}H_3$), 20.9 ($\underline{C}H_3C$=O), 29.5 ($\underline{C}H_2$Fur), 31.5 ($\underline{C}H_2CC$=O), 50.0 ($OCH_2\underline{C}H$), 55.4 ($\underline{C}C$=O), 62.2 ($\underline{C}H_2CH_3$), 67.3 ($O\underline{C}H_2$), 111.9 ($\underline{C}$H=CHO), 119.1 ($\underline{C}$CH=CHO), 141.3 (CH=$\underline{C}$HO), 143.3 (C=$\underline{C}$HO), 170.7 ($CH_3\underline{C}$=O), 171.3 (C$\underline{C}$=O), 174.6 (N$\underline{C}$=O); *m/z* (CI): 310 (MH^+, 42%), 236 (MH^+ $-CO_2Et$, 90), 222 (19), 203 (47), 190 (43), 81 ($FurCH_2^+$, 100); HRMS (CI): $C_{15}H_{20}NO_6$ (MH^+) requires: 310.1291; found 310.1289.

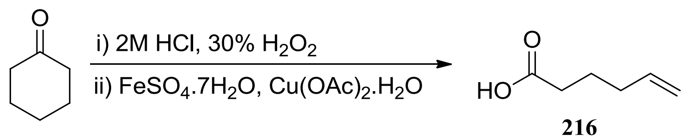
215. (3*R*,5*S*)-Ethyl 5-(acetoxymethyl)-3-(furan-3-ylmethyl)-2-thioxopyrrolidine-3-carboxylate



214 **215**

A stirred solution of lactam **214** (285 mg, 0.922 mmol) in THF (5 mL) was treated with Lawesson's reagent (206 mg, 0.507 mmol) and heated to reflux for 5.5 h. The reaction mixture was treated with further Lawesson's reagent (21 mg, 0.051 mmol) and heated to reflux for 2 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 25-50% Et_2O in petroleum ether) gave thiolactam **215** (197 mg, 65%) as a colourless oil: $[\alpha]_D^{20}$= –0.8 (*c* 1.25, $CHCl_3$); ν_{max}/cm^{-1} (film): 3142 (br, N-H), 2982 (C-H), 2932 (C-H), 2906 (C-H), 1733 (C=O), 1515 (C=S); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 2.08 (3H, s, $C\underline{H}_3C$=O), 2.35-2.42 (2H, m, $C\underline{H}_2CC$=O), 3.11 (1H, d, *J* 14.3 Hz, 1 of $C\underline{H}_2$Fur), 3.26 (1H, d, *J* 14.3 Hz, 1 of $C\underline{H}_2$Fur), 3.60-3.68 (1H, m, $OCH_2C\underline{H}$), 3.98 (1H, dd, *J* 11.3, 9.0 Hz, 1 of $OC\underline{H}_2$), 4.18-4.28 (3H, m, 1 of $OC\underline{H}_2$, $C\underline{H}_2CH_3$), 6.38 (1H, d, *J* 0.9 Hz, $CH_2CC\underline{H}$), 7.26 (1H, s, C=C$\underline{H}$O), 7.34 (1H, s, CH=C$\underline{H}$O), 8.04 (1H, br s, N$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1 ($CH_2\underline{C}H_3$), 20.9 ($\underline{C}H_3C$=O), 32.1 ($\underline{C}H_2$Fur), 33.2 ($\underline{C}H_2CC$=O), 58.4 ($OCH_2\underline{C}H$), 62.3 ($\underline{C}H_2CH_3$), 65.2 ($\underline{C}C$=S), 66.3 ($O\underline{C}H_2$), 112.0 ($\underline{C}$H=CHO), 119.1 ($\underline{C}$CH=CHO), 141.4 (CH=$\underline{C}$HO), 143.2 (C=$\underline{C}$HO), 170.6 ($CH_3\underline{C}$=O), 171.0 (C$\underline{C}$=O), 205.1 (N$\underline{C}$=S); *m/z* (EI): 325 (M^+, 48%), 252 (M^+ –CO_2Et, 100), 210 (M^+ –CH_3CO, 33); HRMS (EI): $C_{15}H_{19}NO_5S$ (M^+) requires: 325.0979; found 325.0973.

216. Hex-5-enoic acid

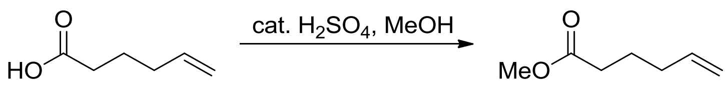


216

Prepared by the method of Cardinale.[89] A stirred solution of cyclohexanone (0.98 g, 10 mmol) in 2M HCl (0.1 mL) was treated dropwise with 30% H_2O_2 (1.13 mL). The reaction mixture was stirred for 40 mins until a white precipitate had formed. The mixture was diluted with H_2O (2 mL) and the precipitate was collected by filtration and washed with

H_2O (3 x 5 mL) with care taken to not allow the precipitate to dry out. A solution of $FeSO_4.7H_2O$ (1.39 g, 5 mmol) in MeOH (20 mL) was treated with $Cu(OAc_2).H_2O$ (1.75 g, 8.77 mmol) and the resulting mixture was cooled to 0 ºC and treated with the hydroxy peroxide and warmed to room temperature overnight. The reaction mixture was reduced in volume to ca. 5 mL then treated with 2M H_2SO_4 solution (5 mL). The mixture was filtered and the precipitate was washed with petroleum ether (10 mL). The filtrate was separated and the MeOH layer was washed with petroleum ether (2 × 15 mL). The combined petroleum ether layers were dried ($MgSO_4$) then concentrated *in vacuo* to give carboxylic acid **216** (519 mg, 49%) as a yellow oil: ν_{max}/cm^{-1} (film): 3078 (br, O-H), 2978 (C-H), 2937 (C-H), 2870 (C-H), 1704 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 1.74 (2H, quin, *J* 7.4 Hz, $CH_2C\underline{H}_2CH_2$), 2.07-2.15 (2H, m, $C\underline{H}_2CH{=}CH_2$), 2.36 (2H, t, *J* 7.2 Hz, $C{=}OC\underline{H}_2$), 5.00 (1H, dd, *J* 10.2, 1.1 Hz, $CH{=}C\underline{H}_2^{cis}$), 5.03 (1H, dq, *J* 16.9, 1.5 Hz, $CH{=}C\underline{H}_2^{trans}$), 5.78 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, $C\underline{H}{=}CH_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.8 ($CH_2\underline{C}H_2CH_2$), 33.0 ($\underline{C}H_2CH{=}CH_2$), 33.3 ($C{=}O\underline{C}H_2$), 115.7 ($CH{=}\underline{C}H_2$), 137.6 ($\underline{C}H{=}CH_2$), 179.7 ($\underline{C}{=}O$).

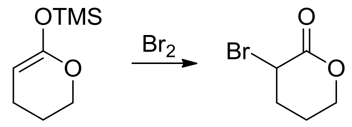
217. Methyl hex-5-enoate[149]



216 **217**

A stirred solution of carboxylic acid **216** (2.8 g, 24.7 mmol) in MeOH (40 mL) was treated with conc. H_2SO_4 (1 drop) and heated to reflux for 3 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petroleum ether) gave ester **217** (876 mg, 28%) as a colourless oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2932 (C-H), 2857 (C-H), 1739 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 1.73 (2H, quin, *J* 7.4 Hz, $CH_2C\underline{H}_2CH_2$), 2.08 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CH{=}CH_2$), 2.32 (2H, t, *J* 7.5 Hz, $C{=}OC\underline{H}_2$), 3.66 (3H, s, $C\underline{H}_3O$), 4.98 (1H, d, *J* 10.5 Hz, $CH{=}C\underline{H}_2^{cis}$), 5.02 (1H, dq, *J* 17.1, 1.7 Hz, $CH{=}C\underline{H}_2^{trans}$), 5.77 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, $C\underline{H}{=}CH_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.1 ($CH_2\underline{C}H_2CH_2$), 33.2 ($\underline{C}H_2CH{=}CH_2$), 33.4 ($C{=}O\underline{C}H_2$), 51.6 ($\underline{C}H_3O$), 115.5 ($CH{=}\underline{C}H_2$), 137.8 ($\underline{C}H{=}CH_2$), 174.2 ($\underline{C}{=}O$).

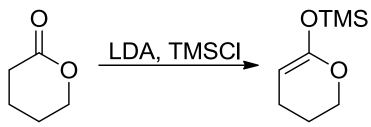
<u>219.</u> 3-Bromotetrahydro-2*H*-pyran-2-one[95]



221 **219**

A stirred solution of silyl enol ether **221** (44 mg, 0.26 mmol) in CH_2Cl_2 (1 mL) was cooled to −15 ºC and treated dropwise with Br_2 (13 µL, 0.255 mmol). The solution was stirred for 30 mins then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 30% Et_2O in petroleum ether) gave lactone **219** (45 mg, 98%) as a colourless oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2944 (C-H), 2876 (C-H), 2861 (C-H), 1733 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 1.85-1.94 (1H, m, 1 of $C\underline{H}_2CH_2O$), 2.21-2.30 (1H, m, 1 of $C\underline{H}_2CH_2O$), 2.31-2.39 (1H, m, 1 of $CHBrC\underline{H}_2$), 2.42-2.51 (1H, m, 1 of $CHBrC\underline{H}_2$), 4.40 (1H, ddd, *J* 11.3, 9.0, 4.5 Hz, $C\underline{H}Br$), 4.56-4.63 (2H, m, $C\underline{H}_2O$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.0 ($\underline{C}H_2CH_2O$), 30.4 ($CHBr\underline{C}H_2$), 40.8 ($\underline{C}HBr$), 70.0 ($\underline{C}H_2O$), 166.9 ($\underline{C}$=O); *m/z* (CI): 181/179 (MH^+, 78%, 81), 101, 99 (MH^+ –HBr, 100); HRMS (CI): $C_5H_8{}^{79}BrO_2$ (MH^+) requires: 178.9708; found 178.9702.

<u>221.</u> ((3,4-Dihydro-2*H*-pyran-6-yl)oxy)trimethylsilane

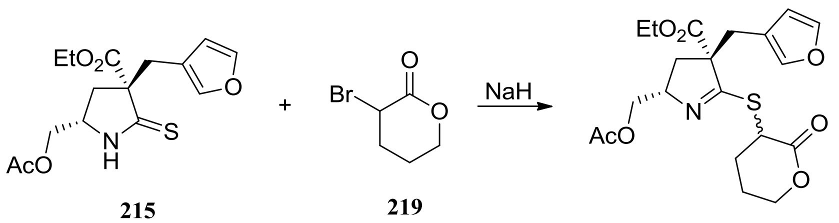


221

Prepared by the method of Christoffers.[91] A stirred solution of diisopropylamine (1.7 mL, 12 mmol) in THF (10 mL) was cooled to 0 ºC and treated dropwise with *n*-butyllithium (2.5 M in hexanes, 4.4 mL, 11 mmol) and stirred for 15 mins then cooled to −78 ºC. The solution was treated with δ–valerolactone (0.93 mL, 10 mmol) in THF (1 mL) and stirred for 15 mins. The reaction mixture was treated with TMSCl (1.7 mL, 13 mmol) and stirred for 1 h then warmed to room temperature. The mixture was concentrated *in vacuo* and diluted with pentane (10 mL), filtered then concentrated *in vacuo*. Purification by distillation (31-32 ºC, 4 mmHg) gave silyl enol ether **221** (1.32 g, 77 %) as a colourless oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2956 (C-H), 2899 (C-H), 2878 (C-H); ^1H NMR (600 MHz, $CDCl_3$) δ 0.21 (9H, s, $C(C\underline{H}_3)_3$), 1.71-1.78 (2H, m, $C\underline{H}_2CH_2O$), 2.00-2.06 (2H, m, C=CHC<u>H</u>$_2$), 3.81 (1H, t, *J* 3.6 Hz, C=C<u>H</u>), 4.03-4.06 (2H, m, C<u>H</u>$_2$O); ^{13}C NMR (150 MHz, $CDCl_3$) δ 0.1 (<u>C</u>(CH_3)$_3$), 20.0 (C(<u>C</u>H_3)$_3$), 22.5 (<u>C</u>H_2CH$_2$O), 67.3 (<u>C</u>H_2O), 74.1 (C=<u>C</u>H), 154.6 (<u>C</u>=CH).

<u>222.</u> (2*S*,4*R*)-Ethyl 2-(acetoxymethyl)-4-(furan-3-ylmethyl)-5-((2-oxotetrahydro-2*H*-pyran-3-yl)thio)-3,4-dihydro-2*H*-pyrrole-4-carboxylate

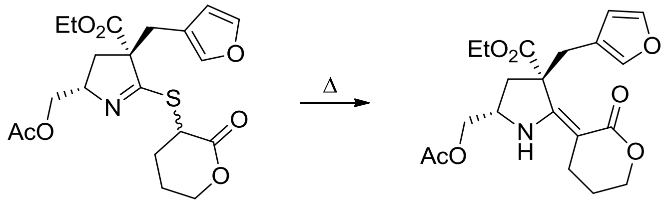
[Major diastereoisomer (MAJ): Minor diastereoisomer (MIN) = 62:38]



NaH (60% dispersion in oil, 58 mg, 1.45 mmol) was washed with hexanes to remove the oil then suspended in THF (7 mL) and cooled to 0 ºC was treated dropwise with thiolactam **215** (394 mg, 1.21 mmol) in THF (2 mL) then stirred for 30 mins. The reaction mixture was treated dropwise with lactone **219** (234 mg, 1.31 mmol) in THF (1 mL) then warmed to room temperature. The reaction mixture was stirred for 1.5 h then diluted with H_2O (12 mL). The organic material was extracted with EtOAc (4 × 15 mL) and the organic extracts were combined, washed with brine (2 × 15 mL), dried ($MgSO_4$) then concentrated *in vacuo* to give thioimidate **222** (340 mg, 66%) as a brown oil which was used in the next step without further purification: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2924 (C-H), 2872 (C-H), 2854 (C-H), 1729 (C=O); ^{1}H NMR (600 MHz; $CDCl_3$): δ 1.30 (1.86H, t, *J* 7.1 Hz, CH$_2$C<u>H</u>$_3$^{MAJ}), 1.31 (1.14H, t, *J* 7.2 Hz, CH$_2$C<u>H</u>$_3$^{MIN}), 1.88-2.00 (2H, m, C<u>H</u>$_2$CH$_2$O$^{MAJ, MIN}$), 2.04 (1.86H, s, C<u>H</u>$_3$CO^{MAJ}), 2.05 (1.14H, s, C<u>H</u>$_3$CO^{MIN}), 2.16 (0.62H, dd, *J* 13.3, 8.4 Hz, 1 of C<u>H</u>$_2$CC=N ^{MAJ}), 2.20 (0.38H, dd, *J* 13.4, 8.0 Hz, 1 of C<u>H</u>$_2$CC=N^{MIN}), 2.24-2.35 (2H, m, 1 of C<u>H</u>$_2$CC=N^{MAJ}, 1 of C<u>H</u>$_2$CC=N ^{MIN}, C<u>H</u>$_2$CHS$^{MAJ, MIN}$), 2.91 (0.62H, d, *J* 14.8 Hz, 1 of C<u>H</u>$_2$CH=CH^{MAJ}), 2.92 (0.38H, d, *J* 14.8 Hz, 1 of C<u>H</u>$_2$CH=CH^{MIN}), 3.07 (0.62H, d, *J* 14.8 Hz, 1 of C<u>H</u>$_2$CH=CH^{MAJ}), 3.08 (0.38H, d, *J* 14.8 Hz, 1 of C<u>H</u>$_2$CH=CH^{MIN}), 3.87-3.93 (1.38H, m, C<u>H</u>S^{MIN}, C<u>H</u>N$^{MAJ, MIN}$), 4.07 (0.62H, dd, *J* 11.2, 6.2 Hz, 1 of OC<u>H</u>$_2$CHN^{MAJ}), 4.13 (0.38H, dd, *J* 11.0, 6.2 Hz, 1 of OC<u>H</u>$_2$CHN^{MIN}), 4.18-4.28 (3H, m, 1 of OC<u>H</u>$_2$CHN^{MAJ}, 1 of OC<u>H</u>$_2$CHN^{MIN}, C<u>H</u>$_2$CH$_3$^{MAJ}, C<u>H</u>$_2$CH$_3$^{MIN}), 4.37-4.47 (2H, m, C<u>H</u>S^{MAJ}, 1 of CH$_2$C<u>H</u>$_2$O^{MAJ}, CH$_2$C<u>H</u>$_2$O^{MIN}), 4.53 (0.62H, dt, *J* 10.8, 4.3

Hz, 1 of $CH_2C\underline{H}_2O^{MAJ}$), 6.34 (0.38H, d, *J* 1.8 Hz, $C\underline{H}{=}CHO^{MIN}$), 6.35 (0.62H, d, *J* 1.8 Hz, $C\underline{H}{=}CHO^{MAJ}$), 7.30 (0.62H, s, $CH_2C{=}C\underline{H}O^{MAJ}$), 7.31 (0.38H, s, $CH_2C{=}C\underline{H}O^{MIN}$), 7.33 (0.62H, s, $CH{=}C\underline{H}O^{MAJ}$), 7.34 (0.38H, s, $CH{=}C\underline{H}O^{MIN}$); ^{13}C NMR (150 MHz; $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3{}^{MIN}$), 14.2 ($CH_2\underline{C}H_3{}^{MAJ}$), 21.03 ($\underline{C}H_3CO^{MAJ}$), 21.04 ($\underline{C}H_3CO^{MIN}$), 23.0 ($\underline{C}H_2CH_2O^{MIN}$), 24.0 ($\underline{C}H_2CH_2O^{MAJ}$), 27.2 ($\underline{C}H_2CHS^{MIN}$), 27.8 ($\underline{C}H_2CHS^{MAJ}$), 30.5 ($\underline{C}H_2CH{=}CH^{MAJ}$), 30.7 ($\underline{C}H_2CH{=}CH^{MIN}$), 35.7 ($\underline{C}H_2CC{=}N^{MAJ}$), 35.9 ($\underline{C}H_2CC{=}N^{MIN}$), 43.9 ($\underline{C}HS^{MAJ}$), 44.1 ($\underline{C}HS^{MIN}$), 62.05 ($\underline{C}H_2CH_3{}^{MAJ}$), 62.13 ($\underline{C}H_2CH_3{}^{MIN}$), 66.3 ($\underline{C}C{=}N^{MAJ}$), 66.58 ($\underline{C}C{=}N^{MIN}$), 66.60 ($O\underline{C}H_2CHN^{MAJ}$), 66.7 ($O\underline{C}H_2CHN^{MIN}$), 69.1 ($CH_2\underline{C}H_2O^{MIN}$), 69.5 ($CH_2\underline{C}H_2O^{MAJ}$), 69.8 ($\underline{C}HN^{MIN}$), 70.0 ($\underline{C}HN^{MAJ}$), 111.7 ($\underline{C}H{=}CHO^{MAJ}$), 111.8 ($\underline{C}H{=}CHO^{MIN}$), 118.9 ($C\underline{C}H{=}CHO^{MAJ}$), 119.0 ($C\underline{C}H{=}CHO^{MIN}$), 141.2 ($CH_2C{=}\underline{C}HO^{MIN}$), 141.4 ($CH_2C{=}\underline{C}HO^{MAJ}$), 143.1 ($CH{=}\underline{C}HO^{MIN}$), 143.3 ($CH{=}\underline{C}HO^{MAJ}$), 168.9 ($CH\underline{C}{=}O^{MAJ}$), 169.3 ($CH\underline{C}{=}O^{MIN}$), 170.2 ($C\underline{C}{=}O^{MAJ}$), 170.6 ($C\underline{C}{=}O^{MIN}$), 171.0 ($CH_3\underline{C}{=}O^{MAJ}$), 171.1 ($CH_3\underline{C}{=}O^{MIN}$), 171.3 ($C\underline{C}{=}N^{MAJ}$), 171.4 ($C\underline{C}{=}N^{MIN}$); *m/z* (CI): 424 ($MH^+$, 100%); HRMS (CI): $C_{20}H_{26}NO_7S$ (MH^+) requires: 424.1430; found 424.1433.

<u>223.</u> (3*S*,5*S*,*E*)-Ethyl 5-(acetoxymethyl)-3-(furan-3-ylmethyl)-2-(2-oxodihydro-2*H*-pyran-3(4*H*)-ylidene)pyrrolidine-3-carboxylate

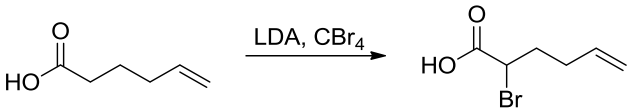


222 **223**

A stirred solution of thioimidate **222** (31 mg, 0.073 mmol) in toluene (2 mL) was heated to 160 ºC in a sealed tube for 18 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 70% Et_2O in petroleum ether) gave amine **223** (23 mg, 81%) as a yellow viscous oil: $[\alpha]_D^{20}$ = +268.6 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} (film): 3364 (br, N-H), 2923 (C-H), 2854 (C-H), 1728 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 1.77-1.89 (2H, m, $C\underline{H}_2CH_2O$), 2.00 (1H, dd, *J* 13.2, 7.9 Hz, 1 of $C\underline{H}_2CC{=}C$), 2.06 (3H, s, $C\underline{H}_3C{=}O$), 2.13-2.21 (2H, m, 1 of $C\underline{H}_2CC{=}C$ and 1 of $C{=}CC\underline{H}_2$), 2.37-2.44 (1H, m, 1 of $C{=}CC\underline{H}_2$), 3.03 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 3.07 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 3.46 (1H, qd, *J* 7.8, 3.8 Hz, $CH_2C\underline{H}N$), 3.82 (1H, dd, *J* 11.3, 7.9 Hz, 1 of $OC\underline{H}_2$), 4.09 (1H, dd, *J* 10.9, 4.1 Hz, 1 of $OC\underline{H}_2$), 4.20-

4.30 (4H, m, $C\underline{H}_2CH_3$ and $CH_2C\underline{H}_2O$), 6.21 (1H, d, *J* 0.8 Hz, $C\underline{H}$=CHO), 7.28 (1H, s, CH_2C=$C\underline{H}O$), 7.33 (1H, t, *J* 1.5 Hz, CH=$C\underline{H}$O), 9.43 (1H, s, $N\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3 ($CH_2\underline{C}H_3$), 20.9 ($\underline{C}H_3C$=O), 23.0 (C=$C\underline{C}H_2$), 23.2 ($\underline{C}H_2CH_2O$), 29.4 ($\underline{C}H_2$Fur), 37.1 ($\underline{C}H_2$CC=C), 56.5 ($CH_2\underline{C}HN$), 57.7 ($\underline{C}$C=C), 62.0 ($\underline{C}H_2CH_3$), 67.0 ($O\underline{C}H_2$), 68.4 ($CH_2\underline{C}H_2O$), 83.9 (C=$\underline{C}$C=O), 112.0 ($\underline{C}$H=CHO), 118.7 ($C\underline{C}$H=CHO), 141.3 (CH=$\underline{C}$HO), 143.5 (CH=$\underline{C}$HO), 164.9 ($\underline{C}$=CC=O), 169.7 (C=C$\underline{C}$=O), 170.9 ($CH_3\underline{C}$=O), 173.4 ($\underline{C}$=$OOCH_2CH_3$); *m/z* (CI): 392 (MH^+, 100%); HRMS (CI): $C_{20}H_{26}NO_7$ (MH^+) requires: 392.1909; found 392.1706.

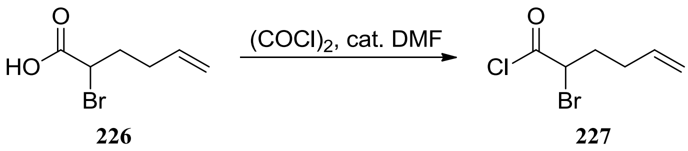
<u>226.</u> 2-Bromohex-5-enoic acid



216 **226**

A stirred solution of diisopropylamine (1.80 mL, 12.8 mmol) in THF (22 mL) was cooled to 0 ºC then treated dropwise with *n*-butyllithium (2.5 M in hexanes, 5.10 mL, 12.8 mmol). The reaction mixture was stirred for 45 mins then cooled to −10 ºC and treated dropwise with carboxylic acid **216** (666 mg, 5.83 mmol) in THF (11 mL) and stirred for 2 h. The reaction mixture was cooled to −78 ºC and treated with CBr_4 (3.9 g, 11.7 mmol) in THF (1 mL) then warmed to room temperature over 1.5 h. The reaction mixture was diluted with brine (30 mL), 2M HCl (30 mL) then extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 30% Et_2O in petroleum ether) gave an oil which was subsequently distilled under reduced pressure (1.3 mmHg, 120 ºC) to give carboxylic acid **226** (517 mg, 46%) as a yellow oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 3081 (br, O-H), 2934 (C-H), 2881 (C-H), 2850 (C-H), 1715 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.03-2.33 (4H, m, $CHBrC\underline{H}_2C\underline{H}_2$), 4.27 (1H, dd, *J* 8.1, 6.2 Hz, $C\underline{H}Br$), 5.06 (1H, d, *J* 10.5 Hz, CH=$C\underline{H}_2^{cis}$), 5.11 (1H, dd, *J* 16.9, 1.5 Hz, CH=$C\underline{H}_2^{trans}$), 5.76 (1H, ddt, *J* 17.1, 10.4, 6.6 Hz, $C\underline{H}$=CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 31.2 ($CHBrCH_2\underline{C}H_2$), 33.7 ($CHBr\underline{C}H_2CH_2$), 44.6 ($\underline{C}HBr$), 116.8 (CH=$\underline{C}H_2$), 135.9 ($\underline{C}$H=CH_2), 174.2 ($\underline{C}$=O); *m/z* (CI): 193/195 (MH^+, 100%), 175/177 (MH^+ −H_2O, 100), 113 (MH^+ −HBr, 97); HRMS (CI): $C_6H_{10}{}^{79}BrO_2$ (MH^+) requires: 192.9864; found 192.9869.

227. 2-Bromohex-5-enoyl chloride

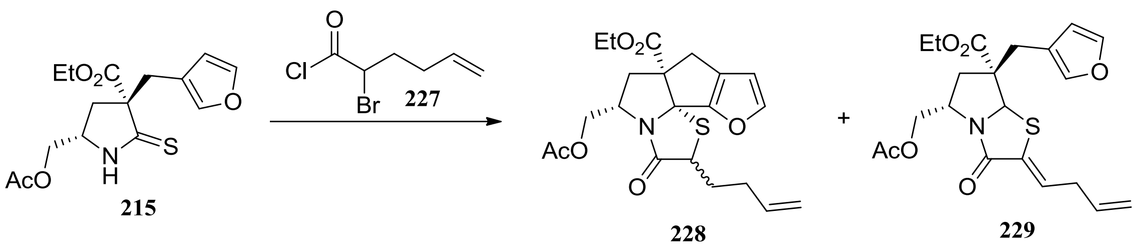


A stirred solution of carboxylic acid **226** (155 mg, 0.803 mmol) in CH_2Cl_2 (3 mL) was treated with $(COCl)_2$ (0.202 mL, 2.41 mmol), DMF (1 drop) and stirred for 1.5 h. The reaction mixture was concentrated *in vacuo* to give acyl chloride **227** (115 mg, 68%) as an oil: ν_{max}/cm^{-1} (film): 2933 (C-H), 2885 (C-H), 2863 (C-H), 1718 (C=O), 1642 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.09-2.18 (1H, m, 1 of CHBrC$\underline{H}_2$), 2.20-2.33 (3H, m, 1 of CHBrC$\underline{H}_2$ and CHBrCH$_2$C$\underline{H}_2$), 4.52 (1H, dd, *J* 8.1, 5.5 Hz, C$\underline{H}$Br), 5.10 (1H, d, *J* 10.4 Hz CH=C$\underline{H}_2^{cis}$), 5.13 (1H, dd, *J* 16.9, 1.1 Hz CH=C$\underline{H}_2^{trans}$), 5.75 (1H, ddt, *J* 16.9, 10.4, 6.4 Hz, C$\underline{H}$=CH$_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 30.9 (CHBrCH$_2\underline{C}$H$_2$), 33.8 (CHBr$\underline{C}$H$_2$), 53.6 ($\underline{C}$HBr), 117.5 (CH=$\underline{C}$H$_2$), 135.3 ($\underline{C}$H=CH$_2$), 170.3 ($\underline{C}$=O). *m/z** (CI): 209/207 (82%), 175/177 (15), 163 (48), 127 (100).

*Mass ion not found

228. (5*S*,6a*R*,10b*R*)-Ethyl 5-(acetoxymethyl)-2-(but-3-enyl)-3-oxo-2,3,5,6,6a,7-hexahydrofuro[3'',2'':4',5']cyclopenta[1',2':2,3]pyrrolo[2,1-b]thiazole-6a-carboxylate

[Major diastereoisomer (MAJ): Minor diastereoisomer (MIN) = 80:20]

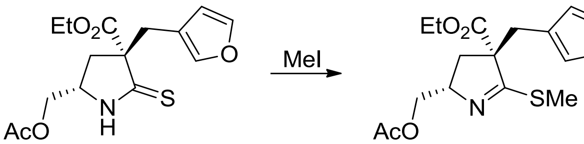


A stirred solution of thiolactam **215** (136 mg, 0.418 mmol) in toluene (2 mL) was treated with acyl chloride **227** (129 mg, 0.610 mmol) in toluene (2 mL). The reaction mixture was heated to reflux for 7 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 10-20% EtOAc in hexane) gave ethyl (3*E*,6*R*,8*S*)-8-acetoxymethyl-3-(but-3-enylidene)-6-(furan-3-ylmethyl)-2-oxo-4-thia-1-azabicyclo[3.3.0

]octane-6-carboxylate **229** (64 mg, 36%) as a yellow oil: $[\alpha]_D^{20}$ = –19.0 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film): 2937 (C-H), 2907 (C-H), 2882 (C-H), 1738 (C=O), 1683 (C=O), 1634 (C=O); ^{1}H NMR (600 MHz; $CDCl_3$): δ 1.30 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 2.08 (3H, s, $C\underline{H}_3CO$), 2.26 (1H, ddd, *J* 14.0, 8.8, 1.6 Hz, 1 of $C\underline{H}_2CCHS$), 2.34 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 2.35 (1H, dd, *J* 14.0, 7.8 Hz, 1 of $C\underline{H}_2CCHS$), 2.90 (2H, br t, *J* 6.4 Hz, $C\underline{H}_2CH{=}CH_2$), 3.20 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 4.11-4.33 (5H, m, $OC\underline{H}_2CHN$, $OCH_2C\underline{H}N$ and $C\underline{H}_2CH_3$), 5.08 (1H, dq, *J* 9.9, 1.3 Hz, $CH{=}C\underline{H}_2^{cis}$), 5.14 (1H, dq, *J* 17.2, 1.6 Hz, $CH{=}C\underline{H}_2^{trans}$), 5.20 (1H, s, $C\underline{H}S$), 5.82 (1H, ddt, *J* 16.9, 10.1, 6.3 Hz, $C\underline{H}{=}CH_2$), 6.13 (1H, s, $C\underline{H}{=}CHO$), 6.78 (1H, t, *J* 7.6 Hz, $C{=}C\underline{H}CH_2$), 7.20 (1H, s, $CH_2C{=}C\underline{H}O$), 7.35 (1H, t, *J* 1.7 Hz, $CH{=}C\underline{H}O$); ^{13}C NMR (150 MHz; $CDCl_3$): δ 14.3 ($CH_2\underline{C}H_3$), 21.0 ($\underline{C}H_3CO$), 25.5 ($\underline{C}H_2$Fur), 33.3 ($\underline{C}H_2CCHS$), 34.7 ($\underline{C}H_2CH{=}CH_2$), 53.4 ($CH_2\underline{C}HN$), 55.1 ($\underline{C}CHS$), 61.9 ($\underline{C}H_2CH_3$), 64.9 ($O\underline{C}H_2CH$), 67.3 ($\underline{C}HS$), 111.5 ($\underline{C}H{=}CHO$), 116.9 ($CH{=}\underline{C}H_2$), 118.6 ($C\underline{C}H{=}CHO$), 126.4 ($O{=}CC{=}\underline{C}H$), 130.9 ($O{=}C\underline{C}{=}CH$), 133.2 ($\underline{C}H{=}CH_2$), 140.9 ($H_2CC{=}\underline{C}HO$), 143.3 ($CH{=}\underline{C}HO$), 166.4 ($O{=}\underline{C}C{=}CH$), 170.8 ($CH_3\underline{C}{=}O$), 172.1 ($O{=}\underline{C}CH_2$); *m/z* (CI): 420 ($MH^+$, 100%); HRMS (CI): $C_{21}H_{26}NO_6S$ (MH^+) requires: 420.1481; found 420.1479. Further elution (20% EtOAc in hexane) gave tetracycle **228** (37 mg, 21%, 4:1 ratio of diastereoisomers) as a yellow oil: ν_{max}/cm^{-1} (film): 2937 (C-H), 2907 (C-H), 2878 (C-H), 1734 (C=O), 1685 (C=O), 1640 (C=O); ^{1}H NMR (600 MHz; $CDCl_3$): δ 1.30 (2.4H, t, *J* 6.8Hz, $CH_2C\underline{H}_3^{MIN}$), 1.32 (0.6H, t, *J* 7.2Hz, $CH_2C\underline{H}_3^{MAJ}$), 1.71-1.78 (0.8H, m, 1 of $SCHC\underline{H}_2^{MAJ}$), 2.06 (2.4H, s, $C\underline{H}_3C{=}O^{MAJ}$), 2.07 (0.6H, s, $C\underline{H}_3C{=}O^{MIN}$), 2.09-2.15 (1.8H, m, $C\underline{H}_2CH{=}CH_2^{MAJ}$ and 1 of $SCHC\underline{H}_2^{MIN}$), 2.15-2.20 (1H, m, 1 of $C\underline{H}_2CCS^{MAJ}$ and 1 of $C\underline{H}_2CCS^{MIN}$), 2.21-2.37 (1.4H, m, 1 of $SCHC\underline{H}_2^{MAJ}$ and 1 of $SCHC\underline{H}_2^{MIN}$, $C\underline{H}_2CH{=}CH_2^{MIN}$), 2.60 (0.2H, d, *J* 15.1 Hz, 1 of $C\underline{H}_2Fur^{MIN}$), 2.61 (0.8H, d, *J* 15.4 Hz, 1 of $C\underline{H}_2Fur^{MAJ}$), 2.89 (0.2H, dd, *J* 13.4, 8.7 Hz, 1 of $C\underline{H}_2CCS^{MIN}$), 2.99 (0.8H, dd, *J* 13.6, 8.7 Hz, 1 of $C\underline{H}_2CCS^{MAJ}$), 3.36 (0.8H, d, *J* 15.4 Hz, 1 of $C\underline{H}_2Fur^{MAJ}$), 3.40 (0.2H, d, *J* 15.1 Hz, 1 of $C\underline{H}_2Fur^{MIN}$), 3.73 (0.8H, m, $C\underline{H}N^{MAJ}$), 3.77 (0.2H, dd, *J* 10.0, 3.8 Hz, $SC\underline{H}^{MIN}$), 4.14 (0.2H, dd, *J* 11.3, 5.2 Hz, 1 of $OC\underline{H}_2^{MIN}$), 4.18-4.31 (1.4H, m, $C\underline{H}_2CH_3^{MAJ}$, $C\underline{H}_2CH_3^{MIN}$, $C\underline{H}N^{MIN}$ and 1 of $OC\underline{H}_2^{MIN}$), 4.38 (0.8H, dd, *J* 9.3, 3.7 Hz, $SC\underline{H}^{MAJ}$), 4.55 (0.8H, dd, *J* 11.3, 6.7 Hz, 1 of $OC\underline{H}_2^{MAJ}$), 4.92 (0.8H, dd, *J* 11.3, 4.4 Hz, 1 of $OC\underline{H}_2^{MAJ}$), 4.99-5.08 (2H, m, $CH{=}C\underline{H}_2^{MAJ}$ and $CH{=}C\underline{H}_2^{MIN}$), 5.74-5.84 (1H, m, $C\underline{H}{=}CH_2^{MAJ}$ and $C\underline{H}{=}CH_2^{MIN}$), 6.23 (0.8H, d, *J* 2.0 Hz, $C\underline{H}{=}CHO^{MAJ}$), 6.24 (0.2H, d, *J* 2.0 Hz, $C\underline{H}{=}CHO^{MIN}$), 7.43 (0.8H, d, *J* 2.0 Hz, $CH{=}C\underline{H}O^{MAJ}$), 7.47 (0.2H, d, *J* 2.0 Hz, $CH{=}C\underline{H}O^{MIN}$); ^{13}C NMR (150 MHz; $CDCl_3$): δ 14.32 ($CH_2\underline{C}H_3^{MIN}$), 14.36 ($CH_2\underline{C}H_3^{MAJ}$), 21.01 ($\underline{C}H_3CO^{MAJ}$), 21.04 ($\underline{C}H_3CO^{MIN}$), 31.3

($\underline{C}$HCH=CH_2^{MAJ} and $\underline{C}$HCH=CH_2^{MIN}), 31.9 (SCH$\underline{C}H_2^{MIN}$), 32.0 (SCH$\underline{C}H_2^{MAJ}$), 33.4 ($\underline{C}H_2$CH=CH^{MIN}), 34.4 ($\underline{C}H_2$CH=CH^{MAJ}), 42.1 ($\underline{C}H_2CCS^{MAJ}$), 43.1 ($\underline{C}H_2CCS^{MIN}$), 51.1 (S$\underline{C}H^{MAJ}$), 51.9 (S$\underline{C}H^{MIN}$), 55.4 ($\underline{C}HN^{MAJ}$), 56.0 ($\underline{C}HN^{MIN}$), 61.8 (O$\underline{C}H_2^{MAJ}$), 61.95 (O$\underline{C}H_2^{MIN}$), 62.0 ($\underline{C}H_2CH_3^{MIN}$), 62.1 ($\underline{C}H_2CH_3^{MAJ}$), 66.3 ($\underline{C}CS^{MAJ}$), 67.0 ($\underline{C}CS^{MIN}$), 78.0 (C$\underline{C}S^{MAJ}$), 79.4 (C$\underline{C}S^{MIN}$), 108.3 ($\underline{C}$H=$CHO^{MAJ}$), 108.5 ($\underline{C}$H=$CHO^{MIN}$), 116.08 (CH=$\underline{C}H_2^{MAJ}$), 116.13 (CH=$\underline{C}H_2^{MIN}$), 125.8 ($\underline{C}$=$CO^{MAJ}$), 126.6 ($\underline{C}$=$CO^{MIN}$), 136.9 ($\underline{C}$H=$CH_2^{MAJ}$), 137.1 ($\underline{C}$H=$CH_2^{MIN}$), 149.3 (CH=$\underline{C}HO^{MAJ}$), 149.7 (CH=$\underline{C}HO^{MIN}$), 153.4 (C=$\underline{C}O^{MIN}$), 154.5 (C=$\underline{C}O^{MAJ}$), 170.7 (N$\underline{C}$=$O^{MAJ}$), 170.8 ($CH_3\underline{C}$=$O^{MAJ}$), 170.9 ($CH_3\underline{C}$=$O^{MIN}$), 171.8 (N$\underline{C}$=$O^{MIN}$), 171.9 (O=$\underline{C}O^{MAJ}$), 172.0 (O=$\underline{C}O^{MIN}$); *m/z* (CI): 420 ($MH^+$, 100%), 378 (16), 360 ($MH^+$ –HOAc, 52), 292 (22); HRMS (CI): $C_{21}H_{26}NO_6S$ (MH^+) requires: 420.1481; found 420.1475.

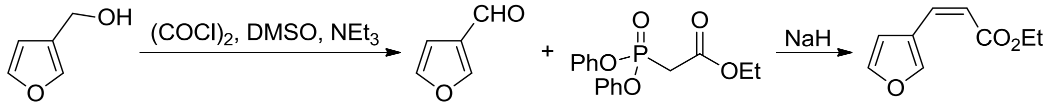
233. (2*S*,4*R*)-Ethyl 2-(acetoxymethyl)-4-(furan-3-ylmethyl)-5-(methylthio)-3,4-dihydro-2*H*-pyrrole-4-carboxylate



215 **233**

A solution of thiolactam **215** (361 mg, 1.11 mmol) in MeCN (1 mL) was treated with MeI (75 µL, 1.21 mmol) and stirred for 3 d. The reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aq. $NaHCO_3$ solution (3 × 10 mL), H_2O (10 mL), brine (10 mL), dried ($MgSO_4$) then concentrated *in vacuo* to give thioimidate **233** (278 mg, 74%) as an oil: $[\alpha]_D^{20}$= –2.2 (*c* 0.9, $CHCl_3$); ν_{max}/cm^{-1} ($CDCl_3$ cast): 2928 (C-H), 2876 (C-H), 2854 (C-H), 1731 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 2.06 (3H, s, $C\underline{H}_3$C=O), 2.18 (1H, dd, *J* 13.6, 7.9 Hz, 1 of $C\underline{H}_2CCS$), 2.32 (1H, dd, *J* 13.6, 6.8 Hz, 1 of $C\underline{H}_2CCS$), 2.46 (3H, s, $SC\underline{H}_3$), 2.89 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 3.07 (1H, d, *J* 14.7 Hz, 1 of $C\underline{H}_2$Fur), 3.88-3.95 (1H, m, $OCH_2C\underline{H}$), 4.10 (1H, dd, *J* 11.3, 5.6 Hz, 1 of $OC\underline{H}_2$), 4.17 (1H, dd, *J* 10.9, 6.0 Hz, 1 of $OC\underline{H}_2$), 4.22 (2H, q, *J* 7.0 Hz, $C\underline{H}_2CH_3$), 6.24 (1H, d, *J* 0.9 Hz, $CH_2CC\underline{H}$), 7.25 (1H, s, C=C$\underline{H}$O), 7.32 (1H, t, *J* 1.5 Hz, CH=C$\underline{H}$O); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.136 ($CH_2\underline{C}H_3$) 14.143 ($S\underline{C}H_3$), 21.1 ($\underline{C}H_3$C=O), 30.8 ($\underline{C}H_2$Fur), 36.1 ($\underline{C}H_2CCS$), 62.0 ($\underline{C}H_2CH_3$), 66.7 ($\underline{C}$CS), 67.0 ($O\underline{C}H_2$), 69.9 ($OCH_2\underline{C}H$), 111.7 ($\underline{C}$H=CHO), 119.3 ($\underline{C}$CH=CHO), 141.0 (CH=$\underline{C}$HO), 143.1 (C=<u>C</u>HO), 171.2 (CH_3<u>C</u>=O), 171.8 (C<u>C</u>=O), 173.9 (br, N=<u>C</u>); *m/z* (CI): 340 (M^+, 100%); HRMS (CI): $C_{16}H_{22}NO_5S$ (M^+) requires: 340.1213; found 340.1209.

<u>242.</u> (*Z*)-Ethyl 3-(furan-3-yl)prop-2-enoate

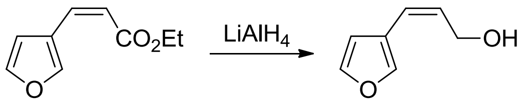


164 **241** **244** **242**

A stirred solution of $(COCl)_2$ (0.343 mL, 3.86 mmol) in CH_2Cl_2 (7.4 mL) was cooled to −78 ºC and treated dropwise with DMSO (0.524 mL, 7.37 mmol). The reaction mixture was stirred for 10 mins then treated dropwise with alcohol **164** (344 mg, 3.51 mmol) in CH_2Cl_2 (5.3 mL) and stirred for 15 mins. The reaction mixture was treated with NEt_3 (2.45 mL, 17.6 mmol), stirred for 5 mins, then warmed to room temperature over 30 mins. The reaction mixture was diluted with H_2O (10 mL) and the organic material extracted with CH_2Cl_2 (2 × 30 mL). The organic extracts were combined and washed with brine (30 mL), dried ($MgSO_4$) then concentrated *in vacuo* to give aldehyde **241** which was used without further purification: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.80 (1H, d, *J* 1.9 Hz, C<u>H</u>=CHO), 7.49 (1H, s, C=C<u>H</u>O), 8.08 (1H, s, CH=C<u>H</u>O), 9.95 (1H, s, O=C<u>H</u>). NaH (60% dispersion in oil, 170 mg, 4.23 mmol) was washed with hexanes to remove the oil then suspended in THF (25 mL) and cooled to 0 ºC was treated with phosphonate **244** (1.23 g, 3.86 mmol) in THF (20 mL) then stirred for 15 mins. The stirred suspension was treated with aldehyde **241** in THF (25 mL) then stirred at 0 °C for 1 h then at room temperature for 45 mins. The mixture was reduced in volume by a third then diluted with saturated aq. NH_4Cl solution (70 mL), H_2O (70 mL) and the organic material extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 3% Et_2O in petroleum ether) gave ester **242** (281 mg, 48%) as a colourless oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2982 (C-H), 2934 (C-H), 2905 (C-H), 1715 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.31 (3H, t, *J* 7.2 Hz, CH_2C<u>H_3</u>), 4.21 (2H, q, *J* 7.2 Hz, C<u>H_2</u>CH_3), 5.80 (1H, d, *J* 12.4 Hz, CH=C<u>H</u>C=O), 6.70 (1H, d, *J* 12.4 Hz, C<u>H</u>=CHC=O), 6.93 (1H, d, *J* 1.9 Hz, C<u>H</u>=CHO), 7.40 (1H, t, *J* 1.5 Hz, CH=C<u>H</u>O), 8.12 (1H, d, *J* 0.8 Hz, C=C<u>H</u>O); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4 (CH_2<u>C</u>H_3), 60.2 (<u>C</u>H_2CH_3), 112.4 (<u>C</u>H=CHO), 116.9 (CH=<u>C</u>HC=O), 121.4 (<u>C</u>=CHO), 133.7

(<u>C</u>H=CHC=O), 143.0 (CH=<u>C</u>HO), 147.1 (C=<u>C</u>HO), 166.4 (<u>C</u>=O); *m/z* (EI): 166 (M^+, 100%), 138 ($M^+-C_2H_4$, 18), 93 (M^+-CO_2Et, 31), 82 (52); HRMS (EI): $C_9H_{10}O_3$ (M^+) requires: 166.0625; found 166.0627.

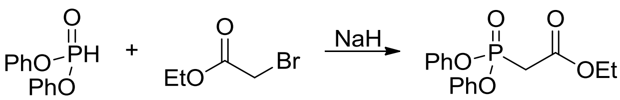
<u>243.</u> (*Z*)-3-(furan-3-yl)prop-2-en-1-ol



242 **243**

A stirred solution of ester **242** (44 mg, 0.265 mmol) in Et_2O (1 mL) was cooled to 0 ºC and treated with $LiAlH_4$ (20 mg, 0.530 mmol). The reaction mixture was stirred at room temperature for 1.5 h then cooled to 0 ºC and quenched with H_2O (2 drops). The mixture was stirred for 30 mins and dried (Na_2SO_4), filtered then concentrated *in vacuo* to give alcohol **243** (31 mg, 94%) as a colourless oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 3340 (br, O-H), 2922 (C-H), 2901 (C-H), 2860 (C-H); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.40 (2H, dd, *J* 6.2, 1.3 Hz, C<u>H</u>$_2$OH), 5.79 (1H, dt, *J* 11.7, 6.0 Hz, CH=C<u>H</u>CH$_2$), 6.30 (1H, d, *J* 11.7 Hz, C<u>H</u>=CHCH$_2$), 6.42 (1H, d, *J* 1.1 Hz, C<u>H</u>=CHO), 7.40 (1H, t, *J* 1.5 Hz, CH=C<u>H</u>O), 7.41 (1H, s, C=C<u>H</u>O); ^{13}C NMR (150 MHz, $CDCl_3$) δ 60.1 (C<u>H</u>$_2$OH), 110.9 (C<u>H</u>=CHO), 121.0 (<u>C</u>H=CHCH$_2$), 121.8 (<u>C</u>=CHO), 130.0 (CH=<u>C</u>HCH$_2$), 141.6 (C=<u>C</u>HO), 143.3 (CH=<u>C</u>HO); *m/z* (CI): 124 (M^+, 15%), 107 (M^+ –OH, 100); HRMS (CI): $C_7H_8O_2$ (M^+) requires: 124.0524; found 124.0528.

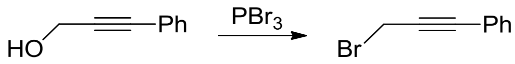
<u>244.</u> Ethyl 2-(diphenoxyphosphonyl)acetate



244

Prepared by the method of Brückner.[150] NaH (60% dispersion in oil, 2.06 g, 51.2 mmol) was washed with hexanes to remove the oil then suspended in THF (200 mL) and cooled to 0 ºC was treated with diphenyl phosphite (8.20 mL, 42.7 mmol) over 15 mins then stirred for 1 h. The reaction mixture was treated dropwise with ethyl bromoacetate (4.50 mL, 40.6 mmol) over 1 h then stirred at room temperature overnight. The reaction mixture was diluted with saturated aq. NH_4Cl solution (100 mL), H_2O (100 mL) and the organic material extracted with Et_2O (3 × 100 mL). The organic extracts were dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 10-30% EtOAc in petroleum ether) gave phosphonate **244** (9.3 g, 68%) as a colourless oil: ν_{max}/cm^{-1} (film): 2983 (C-H), 2934 (C-H), 2873 (C-H), 1735 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 1.28 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 3.27 (2H, d, *J* 21.8 Hz, $PC\underline{H}_2$), 4.23 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CH_3$), 7.17-7.25 (6H, m, aromatic C<u>H</u>), 7.31-7.37 (4H, m, aromatic C<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2 ($CH_2\underline{C}H_3$), 34.2 (d, $^1J_{CP}$ 136.5 Hz, $P\underline{C}H_2$), 62.2 ($\underline{C}H_2CH_3$), 120.8 (d, $^3J_{CP}$ 4.8 Hz, aromatic <u>C</u>H), 125.7 (aromatic <u>C</u>H), 130.0 (aromatic <u>C</u>H), 150.1 (d, $^2J_{CP}$ 8.3 Hz, aromatic <u>C</u>), 164.9 (d, $^2J_{CP}$ 6.6 Hz, <u>C</u>=O).

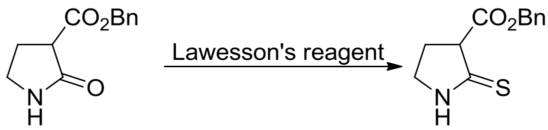
<u>253.</u> (3-Bromoprop-1-yn-1-yl)benzene[112]



253

A stirred solution of 3-phenyl-2-propyn-1-ol (642 mg, 4.86 mmol) in Et_2O (4 mL) at 0 ºC was treated with PBr_3 (0.913 mL, 9.72 mmol). The reaction mixture was stirred for 110 mins then diluted with Et_2O (20 mL). The diluted mixture was washed with H_2O (10 mL), saturated aq. $NaHCO_3$ solution (10 mL), brine (10 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 7% Et_2O in petroleum ether) gave propargyl bromide **253** (431 mg, 45%) as a yellow oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 3001 (C-H), 2951 (C-H), 2924 (C-H), 2219 (C≡C); ^1H NMR (600 MHz, $CDCl_3$) δ 4.17 (2H, s, $C\underline{H}_2Br$), 7.29-7.36 (3H, m, aromatic C<u>H</u>), 7.42-7.47 (2H, m, aromatic C<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.5 ($\underline{C}H_2Br$), 84.3 ($C{\equiv}\underline{C}CH_2Br$), 86.8 ($\underline{C}{\equiv}CCH_2Br$), 122.2 (aromatic <u>C</u>), 128.5 (aromatic <u>C</u>H), 129.0 (aromatic <u>C</u>H), 132.0 (aromatic <u>C</u>H).

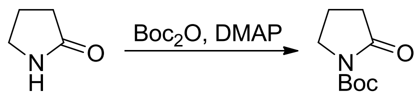
<u>254.</u> Benzyl 2-thioxopyrrolidine-3-carboxylate



257 **254**

A stirred solution of lactam **257** (501 mg, 2.29 mmol) in THF (5.5 mL) was treated with Lawesson's reagent (509 mg, 1.26 mmol), heated to 60 ºC for 4h 15 mins then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50% to 70% EtOAc in petroleum ether) gave thiolactam **254** (419 mg, 78%) as a colourless solid: m.p. 96-97 ºC; ν_{max}/cm^{-1} ($CDCl_3$ cast): 3167 (br, N-H), 2973 (C-H), 2909 (C-H), 2885 (C-H), 1723 (C=O), 1538 (C=S); ^1H NMR (600 MHz, $CDCl_3$) δ 2.45-2.52 (1H, m, 1 of $C\underline{H}_2CH_2N$), 2.54-2.61 (1H, m, 1 of $C\underline{H}_2CH_2N$), 3.61-3.69 (1H, m, 1 of $C\underline{H}_2N$), 3.78-3.83 (1H, m, 1 of $C\underline{H}_2N$), 3.87 (1H, dd, *J* 9.0, 6.0 Hz, $C\underline{H}C{=}S$), 5.23 (2H, s, $C\underline{H}_2Ph$), 7.30-7.44 (5H, m, aromatic $C\underline{H}$), 7.67 (1H, s, $N\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.7 ($\underline{C}H_2CH_2N$), 48.6 ($\underline{C}H_2N$), 58.8 ($\underline{C}HC{=}S$), 67.7 ($\underline{C}H_2Ph$), 128.4 (aromatic $\underline{C}H$), 128.5 (aromatic $\underline{C}H$), 128.7 (aromatic $\underline{C}H$), 135.5 (aromatic $\underline{C}$), 169.8 ($\underline{C}{=}OOCH_2Ph$), 201.0 ($CH\underline{C}{=}SN$); *m/z* (EI): 235 (M^+, 21%), 101 (MH^+ $-CO_2Bn$, 87), 91 ($C_7H_7^+$, 100), 84 (57); HRMS (EI): $C_{12}H_{13}NO_2S$ (M^+) requires: 235.0662; found 235.0671.

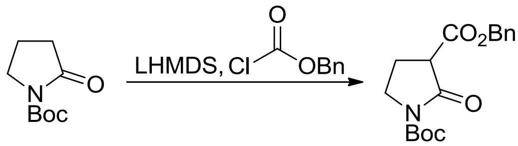
<u>255.</u> *tert*-Butyl 2-oxopyrrolidine-1-carboxylate[113]



255

A stirred solution of pyrrolidin-2-one (2.22 mL, 29.2 mmol) in MeCN (15 mL) at 0 ºC was treated with a solution of Boc_2O (6.64 g, 30.4 mmol) in MeCN (10 mL) followed by DMAP (36 mg, 0.292 mmol) then warmed to room temperature. After stirring for 3 h, the reaction mixture was concentrated *in vacuo* and partitioned between EtOAc (25 mL) and H_2O (25 mL). The biphasic mixture was neutralised with 1M HCl solution and the organic material extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 90% EtOAc in petroleum ether) gave lactam **255** (5.19 g, 96%) as a pale yellow oil: ν_{max}/cm^{-1} (film): 2980 (C-H), 2931 (C-H), 2908 (C-H), 1783, 1751 (C=O), 1712 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 1.51 (9H, s, $C(C\underline{H}_3)_3$), 1.98 (2H, quin, *J* 7.5 Hz, $C\underline{H}_2CH_2N$), 2.50 (2H, t, *J* 8.1 Hz, $C\underline{H}_2C{=}O$), 3.73 (2H, t, *J* 7.2 Hz, $C\underline{H}_2N$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.5 ($\underline{C}H_2CH_2N$), 28.1 ($C(\underline{C}H_3)_3$), 33.1 ($\underline{C}H_2C{=}O$), 46.6 ($\underline{C}H_2N$), 82.9 ($\underline{C}(CH_3)_3$), 150.4 ($N\underline{C}{=}O$), 174.5 ($CH_2\underline{C}{=}O$).

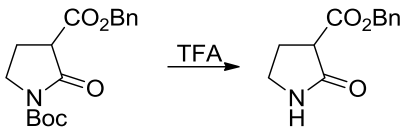
<u>256.</u> 3-Benzyl 1-*tert*-butyl 2-oxopyrrolidine-1,3-dicarboxylate



255 **256**

A stirred solution of HMDS (180 µL, 0.860 mmol) in THF (1.5 mL) at −78 ºC was treated with *n*-butyllithium (2.5 M in hexanes, 0.330 mL, 0.821 mmol) then stirred for 30 mins. The solution was treated with lactam **255** (145 mg, 0.782 mmol) in THF (2.5 mL) and stirred for 1 h then treated with further *n*-butyllithium (2.5 M in hexanes, 0.330 mL, 0.821 mmol) and benzyl chloroformate (0.223 mL, 1.56 mmol). After 30 mins the reaction mixture was warmed to room temperature then stirred for 15 mins. The reaction mixture was quenched with saturated aq. NH_4Cl solution (10 mL) and the organic material extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 15-20% EtOAc in petroleum ether) gave lactam **256** (166 mg, 66%) as a yellow oil which solidified upon storage at 4 ºC: m.p 67-69 ºC; ν_{max}/cm^{-1} ($CDCl_3$ cast): 2982 (C-H), 2941 (C-H), 2915 (C-H), 1787 (C=O), 1756 (C=O), 1731 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.53 (9H, s, $C(C\underline{H}_3)_3$), 2.19-2.28 (1H, m, 1 of $C\underline{H}_2CH_2N$), 2.35-2.43 (1H, m, 1 of $C\underline{H}_2CH_2N$), 3.59 (1H, dd, *J* 9.0, 7.5 Hz, $C\underline{H}C{=}O$), 3.66-3.73 (1H, m, 1 of $C\underline{H}_2N$), 3.88 (1H, ddd, *J* 10.9, 8.7, 5.3 Hz, 1 of $C\underline{H}_2N$), 5.21 (2H, s, $C\underline{H}_2Ph$), 7.30-7.40 (5H, m, aromatic C$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 ($\underline{C}H_2CH_2N$), 28.1 ($C(\underline{C}H_3)_3$), 45.0 ($\underline{C}H_2N$), 50.4 ($\underline{C}HC{=}O$), 67.7 ($\underline{C}H_2Ph$), 83.6 ($\underline{C}(CH_3)_3$), 128.3 (aromatic $\underline{C}$H), 128.5 (aromatic $\underline{C}$H), 128.7 (aromatic $\underline{C}$H), 135.3 (aromatic $\underline{C}$), 150.0 ($N\underline{C}{=}O$), 168.7 ($\underline{C}{=}OOCH_2Ph$), 168.7 ($CH\underline{C}{=}ON$); *m/z* (ES^+): 342 (MNa^+, 100%), 283 (95); HRMS (ES^+): $C_{17}H_{21}NO_5Na$ (MNa^+) requires: 342.1317; found 342.1326.

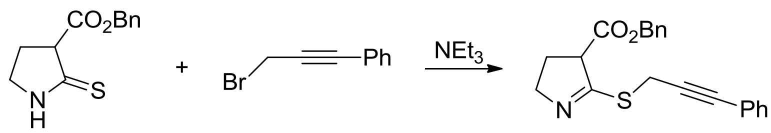
<u>257.</u> Benzyl 2-oxopyrrolidine-3-carboxylate



256 **257**

A stirred solution of lactam **256** (780 mg, 2.44 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (0.544 mL, 7.33 mmol) and stirred for 4h 10 mins. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (10 mL) and the organic material extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) then concentrated *in vacuo* to give lactam **257** (525 mg, 99%) as a colourless solid: m.p. 91-92 ºC; ν_{max}/cm^{-1} ($CDCl_3$ cast): 3241 (br, N-H), 2962 (C-H), 2906 (C-H), 2894 (C-H), 1735 (C=O, ester), 1699 (C=O, amide); ^1H NMR (600 MHz, $CDCl_3$) δ 2.35-2.42 (1H, m, 1 of C<u>H</u>$_2$CH$_2$N), 2.51-2.58 (1H, m, 1 of C<u>H</u>$_2$CH$_2$N), 3.38 (1H, dddd, *J* 9.2, 8.2, 6.1, 0.8 Hz, 1 of C<u>H</u>$_2$N), 3.43 (1H, dd, *J* 9.3, 7.1 Hz, C<u>H</u>C=O), 3.49-3.54 (1H, m, 1 of C<u>H</u>$_2$N), 5.20 (1H, d, *J* 12.4 Hz, 1 of C<u>H</u>$_2$Ph), 5.25 (1H, d, *J* 12.4 Hz, 1 of C<u>H</u>$_2$Ph), 5.93 (1H, s, N<u>H</u>), 7.29-7.41 (5H, m, aromatic C<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.2 (<u>C</u>H$_2$CH$_2$N), 40.7 (<u>C</u>H$_2$N), 47.5 (<u>C</u>HC=O), 67.4 (<u>C</u>H$_2$Ph), 128.3 (aromatic <u>C</u>H), 128.4 (aromatic <u>C</u>H), 128.7 (aromatic <u>C</u>H), 135.6 (aromatic <u>C</u>), 169.9 (<u>C</u>=OOCH$_2$Ph), 173.1 (CH<u>C</u>=ON); *m/z* (CI): 220 (MH^+, 33%), 91 ($C_7H_7^+$, 100); HRMS (CI): $C_{12}H_{14}NO_3$ (MH^+) requires: 220.0974; found 220.0978.

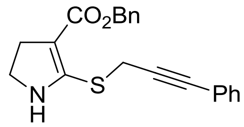
<u>258.</u> Benzyl 5-((3-phenylprop-2-yn-1-yl)thio)-3,4-dihydro-2*H*-pyrrole-4-carboxylate



A flask was charged with propargyl bromide **253** (52 mg, 0.268 mmol), thiolactam **254** (60 mg, 0.255 mmol) and MeCN (0.2 mL) and stirred for 22 h then diluted with MeCN (1 mL). NEt_3 (43 µL, 0.306 mmol) was added to the mixture then diluted with EtOAc (10 mL). The reaction mixture was washed with H_2O (5 mL), dried (Na_2SO_4), then concentrated *in vacuo* to give thioimidate **258** (81 mg, 91 %) as a yellow oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2954 (C-H), 2868 (C-H), 1735 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 2.26-2.34 (1H, m, 1 of C<u>H</u>$_2$CH$_2$N), 2.39-2.47 (1H, m, 1 of C<u>H</u>$_2$CH$_2$N), 3.75-3.82 (1H, m, C<u>H</u>CS), 3.89-3.96 (1H, m, 1 of C<u>H</u>$_2$N), 3.99-4.12 (3H, m, 1 of C<u>H</u>$_2$N and SC<u>H</u>$_2$), 5.17 (1H, d, *J* 12.4 Hz, 1 of C<u>H</u>$_2$Ph), 5.20 (1H, d, *J* 12.4 Hz, 1 of C<u>H</u>$_2$Ph), 7.27-7.44 (10H, m, aromatic C<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.8 (S<u>C</u>H$_2$), 28.7 (<u>C</u>H$_2$CH$_2$N), 56.6 (<u>C</u>HCS), 60.7 (<u>C</u>H$_2$N), 67.5 (<u>C</u>H$_2$Ph), 83.2 (SCH$_2$<u>C</u>≡C), 84.2 (SCH$_2$C≡<u>C</u>), 122.9 (aromatic <u>C</u>), 128.3 (aromatic <u>C</u>H), 128.4 (aromatic <u>C</u>H), 128.46 (aromatic <u>C</u>H), 128.53

(aromatic C̲H), 128.7 (aromatic C̲H), 131.9 (aromatic C̲H), 135.4 (aromatic C̲), 166.7 (br, N=C̲), 170.3 (C̲=O); *m/z* (CI): 350 (MH^+, 100%), 74 (75); HRMS (CI): $C_{21}H_{20}NO_2S$ (MH^+) requires: 350.1215; found 350.1211.

259. Benzyl 2-((3-phenylprop-2-yn-1-yl)thio)-4,5-dihydro-1*H*-pyrrole-3-carboxylate

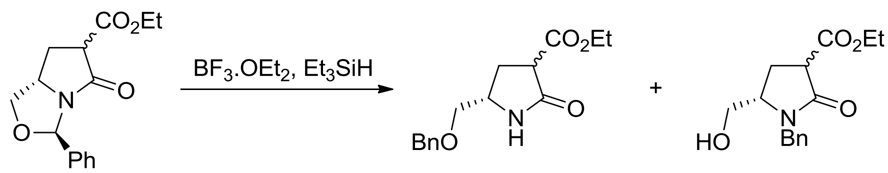


259

Storage of *N*,*S*-ketene acetal **258** at 4 ºC gave a 1:1 mixture of thioimidate **258** and *N*,*S*-ketene acetal **259**; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.21 (1H, ddd, *J* 13.6, 8.7, 7.2 Hz, 1 of C$\underline{H}_2$$CH_2$N), 2.55 (1H, ddd, *J* 13.6, 7.5, 3.0 Hz, 1 of C$\underline{H}_2$$CH_2$N), 3.90 (1H, br s, NH̲), 3.94 (1H, dt, *J* 14.8, 7.5 Hz, 1 of C$\underline{H}_2$N), 4.00 (1H, d, *J* 16.2 Hz, 1 of SC$\underline{H}_2$), 4.05 (1H, d, *J* 16.2 Hz, 1 of SC$\underline{H}_2$), 4.13 (1H, ddd, *J* 14.9, 8.5, 3.0 Hz, 1 of C$\underline{H}_2$N), 5.22 (1H, d, *J* 12.4 Hz, 1 of C$\underline{H}_2$Ph), 5.28 (1H, d, *J* 12.4 Hz, 1 of C$\underline{H}_2$Ph), 7.27-7.44 (10H, m, aromatic CH̲); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.5 (SC̲H_2), 38.0 (C̲$H_2$$CH_2$N), 59.7 (C̲$H_2$N), 68.7 (C̲$H_2$Ph), 83.3 (S$CH_2$C̲≡C), 84.0 (S$CH_2$C≡C̲), 87.5 (C̲=CS), 122.9 (aromatic C̲), 128.1 (aromatic C̲H), 128.3 (aromatic C̲H), 128.4 (aromatic C̲H), 128.805 (aromatic C̲H), 128.810 (aromatic C̲H), 131.9 (aromatic C̲H), 134.7 (aromatic C̲), 170.7 (C=C̲S), 172.8 (C̲=O).

270. (5*S*)-Ethyl 5-((benzyloxy)methyl)-2-oxopyrrolidine-3-carboxylate

[Major diastereoisomer (MAJ): Minor diastereoisomer (MIN) = 54:46]



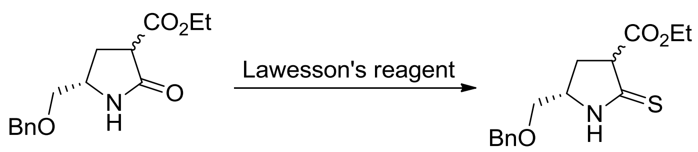
205 **270** **271**

A stirred solution of $BF_3.OEt_2$ (0.155 mL, 1.23 mmol) in CH_2Cl_2 (2 mL) at −78 ºC was treated with a solution of lactam **205** (135 mg, 0.49 mmol) and Et_3SiH (0.195 mL, 1.23 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 3 h and then warmed to room temperature over 2 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (5 mL) and the organic material extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with H_2O (5 mL), dried (hydrophobic frit) then concentrated i*n vacuo*. Purification by MDAP gave lactam **270** (56 mg, 41%, 54:46 mixture of diastereoisomers) as a colourless oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 3241 (br, N-H), 2952 (C-H), 2862 (C-H), 1737 (C=O, ester), 1697 (C=O, amide); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29 (1.38H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3^{MIN}$), 1.30 (1.62H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3^{MAJ}$), 1.99 (0.54H, ddd, *J* 13.3, 9.5, 5.1 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 2.12 (0.46H, ddd, *J* 13.5, 8.0, 6.8 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 2.42 (0.46H, ddd, *J* 13.2, 9.8, 7.9 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 2.59 (0.54H, ddd, *J* 13.6, 8.3, 6.4 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 3.31 (0.54H, dd, *J* 9.4, 7.9 Hz, 1 of $OC\underline{H}_2^{MAJ}$), 3.40-3.46 (1.46H, m, $C\underline{H}C{=}O^{MAJ}$, $C\underline{H}C{=}O^{MIN}$ and 1 of $OC\underline{H}_2^{MIN}$), 3.50 (0.54H, dd, *J* 9.4, 3.8 Hz, 1 of $OC\underline{H}_2^{MAJ}$), 3.58 (0.46H, dd, *J* 9.2, 3.6 Hz, 1 of $OC\underline{H}_2^{MIN}$), 3.83-3.89 (0.46H, m, $C\underline{H}N^{MIN}$), 3.98 (0.54H, tt, *J* 8.0, 4.2 Hz, $C\underline{H}N^{MAJ}$), 4.230 (1.08H, q, *J* 7.2 Hz, $C\underline{H}_2CH_3^{MAJ}$), 4.231 (0.92H, q, *J* 7.2 Hz, $C\underline{H}_2CH_3^{MIN}$), 4.51 (0.46H, d, *J* 11.7 Hz, 1 of $C\underline{H}_2Ph^{MIN}$), 4.52 (1.08H, s, $C\underline{H}_2Ph^{MAJ}$), 4.55 (0.46H, d, *J* 11.7 Hz, 1 of $C\underline{H}_2Ph^{MIN}$), 5.91 (0.54H, br s, $N\underline{H}^{MAJ}$), 6.00 (0.46H, br s, $N\underline{H}^{MIN}$), 7.28-7.39 (5H, m, aromatic $C\underline{H}^{MAJ}$ and aromatic $C\underline{H}^{MIN}$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 14.3 ($CH_2\underline{C}H_3^{MAJ}$ and $CH_2\underline{C}H_3^{MIN}$), 26.8 ($\underline{C}H_2CHC{=}O^{MIN}$), 27.5 ($\underline{C}H_2CHC{=}O^{MAJ}$), 47.51 ($\underline{C}HC{=}O^{MAJ}$), 47.52 ($\underline{C}HC{=}O^{MIN}$), 52.2 ($\underline{C}HN^{MIN}$), 52.5 ($\underline{C}HN^{MAJ}$), 61.9 ($\underline{C}H_2CH_3^{MAJ}$), 62.0 ($\underline{C}H_2CH_3^{MIN}$), 73.5 ($\underline{C}H_2Ph^{MAJ}$), 73.6 ($\underline{C}H_2Ph^{MIN}$), 73.7 ($O\underline{C}H_2^{MAJ}$), 74.2 ($O\underline{C}H_2^{MIN}$), 127.86 (aromatic $\underline{C}H^{MAJ}$), 127.94 (aromatic $\underline{C}H^{MIN}$), 128.1 (aromatic $\underline{C}H^{MAJ}$ and aromatic $\underline{C}H^{MIN}$), 128.68 (aromatic $\underline{C}H^{MIN}$), 128.70 (aromatic $\underline{C}H^{MAJ}$), 137.55 (aromatic $\underline{C}^{MAJ}$), 137.59 (aromatic $\underline{C}^{MIN}$), 169.96 ($\underline{C}{=}O^{MIN}$), 169.98 ($\underline{C}{=}O^{MAJ}$), 172.0 ($N\underline{C}{=}O^{MIN}$), 172.4 ($N\underline{C}{=}O^{MAJ}$) ; *m/z* (CI): 278 (MH^+, 100%), 91 ($C_7H_7^+$, 19); HRMS (CI): $C_{15}H_{20}NO_4$ (MH^+) requires: 278.1392; found 278.1390; and (5*S*)-ethyl 1-benzyl-5-(hydroxymethyl)-2-oxopyrrolidine-3-carboxylate **271** (19 mg, 14%, 68:32 mixture of diastereoisomers) as a colourless solid: m.p. 82-83 ºC; ν_{max}/cm^{-1} ($CDCl_3$ cast): 3420 (br, O-H), 2934 (C-H), 1733 (C=O, ester) 1669 (C=O, amide); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (0.96H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3^{MIN}$), 1.33 (2.04H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3^{MAJ}$), 2.21 (0.32H, ddd, *J* 13.2, 9.4, 4.0 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 2.26 (0.68H, dt, *J* 13.6, 4.9 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 2.37 (0.68H, ddd, *J* 13.6, 10.7, 8.8 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 2.45 (0.32H, ddd, *J* 13.2, 7.9, 7.9 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 3.49 (0.32H, dd, *J* 11.7, 2.6 Hz, 1 of $OC\underline{H}_2^{MIN}$), 3.53 (0.68H, dd, *J* 10.5, 5.6 Hz, $C\underline{H}C{=}O^{MAJ}$), 3.58 (0.68H, m, $C\underline{H}N^{MAJ}$), 3.62 (0.68H, dd, *J* 12.0, 2.6 Hz, 1 of $OC\underline{H}_2^{MAJ}$), 3.65-3.69 (0.64H, m, $C\underline{H}C{=}O^{MIN}$ and $C\underline{H}N^{MIN}$), 3.73 (0.32H, dd, *J* 11.7, 3.0 Hz, 1 of $OC\underline{H}_2^{MIN}$), 3.81 (0.68H, dd, *J* 12.0, 3.4 Hz, 1 of $OC\underline{H}_2^{MAJ}$), 4.20 (0.68H, d, *J* 15.1 Hz, 1 of $C\underline{H}_2Ph^{MAJ}$), 4.23-4.29

(2H, m, $C\underline{H}_2CH_3^{MAJ}$ and $C\underline{H}_2CH_3^{MIN}$), 4.31 (0.32H, d, *J* 15.1 Hz, 1 of $C\underline{H}_2Ph^{MIN}$), 4.80 (0.32H, d, *J* 15.1 Hz, 1 of $C\underline{H}_2Ph^{MIN}$), 4.92 (0.68H, d, *J* 15.1 Hz, 1 of $C\underline{H}_2Ph^{MAJ}$), 7.27-7.37 (5H, m, aromatic $C\underline{H}^{MAJ}$ and aromatic $C\underline{H}^{MIN}$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 14.2 ($CH_2\underline{C}H_3^{MAJ}$), 14.3 ($CH_2\underline{C}H_3^{MIN}$), 24.9 ($\underline{C}H_2CHC{=}O^{MAJ}$), 25.8 ($\underline{C}H_2CHC{=}O^{MIN}$), 45.3 ($\underline{C}H_2Ph^{MAJ}$), 45.4 ($\underline{C}H_2Ph^{MIN}$), 47.8 ($\underline{C}HC{=}O^{MAJ}$), 48.3 ($\underline{C}HC{=}O^{MIN}$), 57.2 ($\underline{C}HN^{MAJ}$), 57.8 ($\underline{C}HN^{MIN}$), 61.8 ($\underline{C}H_2CH_3^{MIN}$), 62.3 ($O\underline{C}H_2^{MIN}$), 62.4 ($\underline{C}H_2CH_3^{MAJ}$), 62.7 ($O\underline{C}H_2^{MAJ}$), 127.9 (aromatic $\underline{C}H^{MIN}$), 128.0 (aromatic $\underline{C}H^{MAJ}$), 128.2 (aromatic $\underline{C}H^{MAJ}$ and aromatic $\underline{C}H^{MIN}$), 128.2 (aromatic $\underline{C}H^{MAJ}$), 129.0 (aromatic $\underline{C}H^{MIN}$), 136.4 (aromatic $\underline{C}^{MAJ}$), 136.5 (aromatic $\underline{C}^{MIN}$), 170.2 ($N\underline{C}{=}O^{MAJ}$), 170.7 ($\underline{C}{=}O^{MIN}$), 171.3 ($N\underline{C}{=}O^{MIN}$), 171.7 ($\underline{C}{=}O^{MAJ}$); *m/z* (CI): 278 (MH^+, 100%); HRMS (CI): $C_{15}H_{20}NO_4$ (MH^+) requires: 278.1392; found 278.1392.

<u>272.</u> (5*S*)-Ethyl 5-((benzyloxy)methyl)-2-thioxopyrrolidine-3-carboxylate

[Major diastereoisomer (MAJ): Minor diastereoisomer (MIN) = 55:45]

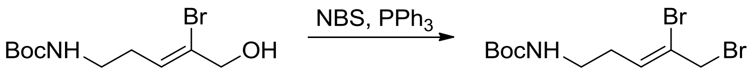


270 **272**

A stirred solution of lactam **270** (49 mg, 0.177 mmol) in THF (1 mL) was treated with Lawesson's reagent (43 mg, 0.106 mmol). The reaction mixture was heated to reflux for 5 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50% TBME in cyclohexane) gave thiolactam **272** (31 mg, 60%, 55:45 mixture of diastereoisomers) as a colourless oil: ν_{max}/cm^{-1} (film): 3175 (br, N-H), 2982 (C-H), 2928 (C-H), 2864 (C-H), 1729 (C=O), 1503 (C=S); ^1H NMR (600 MHz, $CDCl_3$) δ 1.31 (1.35H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3^{MIN}$), 1.32 (1.65H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3^{MAJ}$), 2.07 (0.55H, ddd, *J* 13.2, 9.4, 6.4 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 2.17 (0.45H, dt, *J* 13.2, 7.5 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 2.52 (0.45H, ddd, *J* 13.2, 9.4, 8.3 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 2.58 (0.55H, ddd, *J* 13.1, 8.0, 4.9 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 3.37 (0.55H, dd, *J* 9.4, 8.7 Hz, 1 of $OC\underline{H}_2^{MAJ}$), 3.54 (0.55H, t, *J* 9.4 Hz, 1 of $OC\underline{H}_2^{MAJ}$), 3.56 (0.45H, dd, *J* 9.4, 3.8 Hz, 1 of $OC\underline{H}_2^{MIN}$), 3.62 (0.45H, dd, *J* 9.4, 4.0 Hz, 1 of $OC\underline{H}_2^{MIN}$), 3.83 (0.55H, dd, *J* 9.4, 8.3 Hz, $C\underline{H}C{=}S^{MAJ}$), 3.86 (0.45H, dd, *J* 9.2, 4.7 Hz, $C\underline{H}C{=}S^{MIN}$), 4.10-4.17 (0.45H, m, $C\underline{H}N^{MIN}$), 4.19-4.33 (2.55H, m, $C\underline{H}_2CH_3^{MAJ}$, $C\underline{H}_2CH_3^{MIN}$ and $C\underline{H}N^{MAJ}$), 4.51 (0.45H, d, *J* 11.7 Hz, 1 of $C\underline{H}_2Ph^{MIN}$), 4.52 (0.55H, d, *J*

11.7 Hz, 1 of C$\underline{H}_2$Ph^{MAJ}), 4.55 (0.55H, d, *J* 11.7 Hz, 1 of C$\underline{H}_2$Ph^{MAJ}), 4.58 (0.45H, d, *J* 11.7 Hz, 1 of C$\underline{H}_2$Ph^{MIN}), 7.29-7.39 (5H, m, aromatic C$\underline{H}^{MAJ}$ and aromatic C$\underline{H}^{MIN}$), 8.02 (0.55H, br s, N$\underline{H}^{MAJ}$), 8.06 (0.45H, br s, N$\underline{H}^{MIN}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2 ($CH_2\underline{C}H_3^{MAJ}$), 14.3 ($CH_2\underline{C}H_3^{MIN}$), 29.2 ($\underline{C}H_2$CHC=O^{MIN}), 29.9 ($\underline{C}H_2$CHC=O^{MAJ}), 58.5 ($\underline{C}$HC=S^{MIN}), 58.9 ($\underline{C}$HC=S^{MAJ}), 60.5 ($\underline{C}$HN^{MIN}), 61.0 ($\underline{C}$HN^{MAJ}), 62.0 ($\underline{C}H_2CH_3^{MAJ}$), 62.1 ($\underline{C}H_2CH_3^{MIN}$), 72.1 (O$\underline{C}H_2^{MAJ}$), 72.8 (O$\underline{C}H_2^{MIN}$), 73.66 ($\underline{C}H_2$Ph^{MAJ}), 73.74 ($\underline{C}H_2$Ph^{MIN}), 127.9 (aromatic $\underline{C}$H^{MAJ}), 128.0 (aromatic $\underline{C}$H^{MIN}), 128.2 (aromatic $\underline{C}$H^{MAJ} and aromatic $\underline{C}$H^{MIN}), 128.72 (aromatic $\underline{C}$H^{MIN}), 128.74 (aromatic $\underline{C}$H^{MAJ}), 137.29 (aromatic $\underline{C}^{MAJ}$), 137.34 (aromatic $\underline{C}^{MIN}$), 170.0 ($\underline{C}$=O^{MAJ}), 170.1 ($\underline{C}$=O^{MIN}), 200.4 ($\underline{C}$=S^{MIN}), 200.5 ($\underline{C}$=S^{MAJ}); *m/z* (CI): 294 (MH^+, 100%); HRMS (CI): $C_{15}H_{20}NO_3S$ (MH^+) requires: 294.1164; found 294.1166.

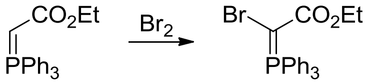
<u>273.</u> (*Z*)-*tert*-Butyl (4,5-dibromopent-3-en-1-yl)carbamate



278 **273**

A stirred solution of alcohol **278** (100 mg, 0.357 mmol) in CH_2Cl_2 (1.75 mL) was treated with PPh_3 (112 mg, 0.428 mmol) and NBS (76 mg, 0.43 mmol). The reaction mixture was stirred overnight then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 0-50% TBME in cyclohexane) gave bromide **273** (94 mg, 77%, 10:1 *Z*:*E*) as a colourless solid: m.p. 27-28 ºC; ν_{max}/cm^{-1} (solid): 3361 (br, N-H), 2980 (C-H), 2934 (C-H), 1680 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44 (9H, s, C(C$\underline{H}_3$)$_3$), 2.40 (2H, q, *J* 6.8 Hz, C$\underline{H}_2$CH=C), 3.23 (2H, br m, NHC$\underline{H}_2$), 4.24 (2H, s, C$\underline{H}_2$Br), 4.57 (1H, br s, N$\underline{H}$), 6.13 (1H, t, *J* 6.9 Hz, C$\underline{H}$=C); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.5 (C($\underline{C}H_3$)$_3$), 32.6 ($\underline{C}H_2$CH=C), 38.6 (NH$\underline{C}H_2$), 38.9 ($\underline{C}H_2$Br), 79.6 ($\underline{C}(CH_3)_3$), 124.6 (CH=$\underline{C}$), 131.4 ($\underline{C}$H=C), 156.0 ($\underline{C}$=O); *m/z* (CI): 342/344/346 (MH^+, 10/20/10%), 286/288/290 (MH^+–$Me_2C=CH_2$, 65/80/64), 206/208 (MH^+–$Me_2C=CH_2$–HBr, 100), 130 ($BocNHCH_2^+$, 95); HRMS (CI): $C_{10}H_{19}{}^{79}BrNO_3$ (MH^+) requires: 280.0548; found 280.0553; anal. calcd. for $C_{10}H_{17}Br_2NO_2$: C, 35.01; H, 4.99; N, 4.08. Found: C, 35.05; H, 5.14; N, 4.01.

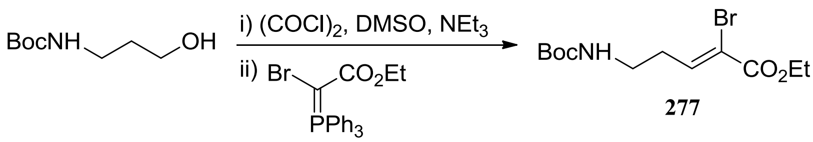
275. Ethyl 2-bromo-2-(triphenylphosphoranylidene)acetate



275

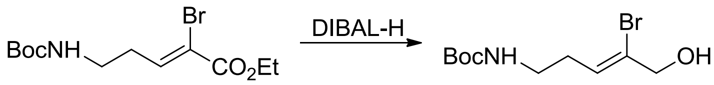
Prepared by the method of Gong.[123] A stirred solution of ethyl 2-(triphenylphosphoranylidene)acetate (2.00 g, 5.74 mmol) in CH_2Cl_2 (10 mL) at 0 ºC was treated with Br_2 (0.3 mL, 6 mmol) in CH_2Cl_2 (5 mL) then stirred overnight. The reaction mixture was washed with H_2O (15 mL), saturated aq. $NaHCO_3$ (2 × 15 mL), dried (Na_2SO_4) then concentrated *in vacuo*. Recrystallisation (acetone/*n*-hexane, 2:1) gave phosphorane **275** (1.83 g, 75% yield) as a yellow solid: m.p. 131-132 ºC [lit.[123] = 148-151 ºC]; ν_{max}/cm^{-1} (solid): 2982 (C-H), 2943 (C-H), 2891 (C-H), 1649 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, br s, $CH_2C\underline{H}_3$), 3.89 (2H, br s, $C\underline{H}_2CH_3$), 7.40-7.70 (15H, m, aromatic C<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 (br, $CH_2\underline{C}H_3$), 27.2 (br, P=<u>C</u>), 59.1 (br, $\underline{C}H_2CH_3$), 126.5 (d, J_{CP} 95.0 Hz, aromatic <u>C</u>), 128.7 (d, J_{CP} 12.7 Hz, aromatic <u>C</u>H), 132.3 (d, J_{CP} 2.4 Hz, aromatic <u>C</u>H), 134.0 (d, J_{CP} 9.6 Hz, aromatic <u>C</u>H), 168.8 (<u>C</u>=O).

277. (*Z*)-Ethyl 2-bromo-5-((*tert*-butoxycarbonyl)amino)pent-2-enoate



A stirred solution of DMSO (1.67 mL, 23.5 mmol) in CH_2Cl_2 (84 mL) at −20 ºC was treated with $(COCl)_2$ (1.03 mL, 11.7 mmol). After stirring for 20 mins the solution was cooled to −78 ºC and treated with a solution of *tert*-butyl(3-hydroxypropyl)carbamate (1.37 g, 7.82 mmol) in CH_2Cl_2 (2 mL). After 1 h the reaction was treated with NEt_3 (3.96 mL, 39.1 mmol) then warmed to room temperature. The reaction mixture was stirred for 30 mins then quenched with H_2O (100 mL) and the organic material extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with H_2O (50 mL), brine (50 mL), dried (Na_2SO_4) then concentrated *in vacuo* to give the crude aldehyde which was dissolved in CH_2Cl_2 (30 mL). Phosphorane **275** (3.34 g, 7.82 mmol) was dissolved in CH_2Cl_2 (30 mL) and treated with the aldehyde solution then stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with H_2O (20 mL) and the organic material extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) then concentrated *in vacuo* to give an oil which was dissolved in Et_2O (100 mL) and filtered. The filtrate was concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50% CH_2Cl_2 in cyclohexane and then 15-30% EtOAc in cyclohexane) gave ester **277** (1.56 g, 62%, 9:1 *Z*:*E*) as a pale yellow oil: ν_{max}/cm^{-1} (film): 3366 (br, N-H), 2978 (C-H), 2933 (C-H), 1714 (C=O, ester), 1692 (C=O, carbamate); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 1.43 (9H, s, $C(C\underline{H}_3)_3$), 2.55 (2H, q, *J* 6.8 Hz, $C\underline{H}_2CH=C$), 3.28-3.35 (2H, m, $NHC\underline{H}_2$), 4.27 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CH_3$), 4.63 (1H, br s, $N\underline{H}$), 7.28 (1H, t, *J* 7.2 Hz, $C\underline{H}=C$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3 ($CH_2\underline{C}H_3$), 28.5 ($C(\underline{C}H_3)_3$), 33.1 ($\underline{C}H_2CH=C$), 38.6 ($NH\underline{C}H_2$), 62.7 ($\underline{C}H_2CH_3$), 79.7 ($\underline{C}(CH_3)_3$), 142.6 ($CH=\underline{C}$), 144.9 ($\underline{C}H=C$), 156.0 ($N\underline{C}=O$), 162.3 ($\underline{C}=OOCH_2$); *m/z* (CI): 322/324 (MH^+, 2%), 266/268 (MH^+–$Me_2C=CH_2$–, 100), 222/224 (MH^+–$Me_2C=CH_2$–CO_2, 84); HRMS (CI): $C_{12}H_{21}{}^{79}BrNO_4$ (MH^+) requires: 322.0654; found 322.0667.

<u>278.</u> (*Z*)-*tert*-Butyl (4-bromo-5-hydroxypent-3-en-1-yl)carbamate

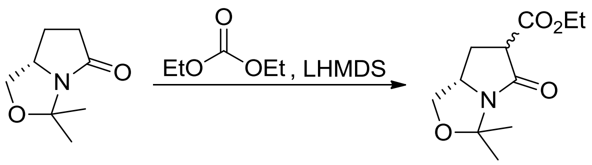


277 **278**

A stirred solution of ester **277** (0.975 g, 3.03 mmol) in THF (15 mL) at −78 ºC was treated with DIBAL-H (9.40 mL, 9.38 mmol) over 5 mins. The reaction mixture was stirred for 75 mins and warmed to 0 ºC then stirred for 45 mins. The reaction mixture was treated with further DIBAL-H (3.00 mL, 3.03 mmol) then stirred for 1 h. MeOH (5 mL) was added and the mixture was diluted with EtOAc (25 mL) and washed with 1M HCl solution (10 mL), H_2O (10 mL), brine (10 mL), dried (Na_2SO_4) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 10-20% EtOAc in cyclohexane) gave alcohol **278** (486 mg, 57%, 8:1 *Z*:*E*) as a colourless oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 3340 (br, O-H), 2978 (C-H), 2930 (C-H), 1687 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.43 (9H, s, $C(C\underline{H}_3)_3$), 2.40 (2H, q, *J* 6.8 Hz, $C\underline{H}_2CH=C$), 3.19-3.27 (2H, br m, $NHC\underline{H}_2$), 4.25 (2H, s, $C\underline{H}_2OH$), 4.63 (1H, br s, $N\underline{H}$), 6.03 (1H, t, *J* 7.0 Hz, $C\underline{H}=C$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.5 ($C(\underline{C}H_3)_3$), 31.7 ($\underline{C}H_2CH=C$), 39.2 ($NH\underline{C}H_2$), 68.3 ($\underline{C}H_2OH$), 79.5 ($\underline{C}(CH_3)_3$), 126.6 ($\underline{C}H=C$), 128.9 ($CH=\underline{C}$), 156.1 ($\underline{C}=O$); *m/z* (CI): 280/282 (MH^+, 20%), 224/226 ($MH^+{-}Me_2C{=}CH_2$, 66), 206/208 ($MH^+{-}$ Me_3COH, 100); HRMS (CI): $C_{10}H_{19}{}^{79}BrNO_3$ (MH^+) requires: 280.0548; found 280.0553.

281. (7a*S*)-Ethyl 3,3-dimethyl-5-oxohexahydropyrrolo[1,2-*c*]oxazole-6-carboxylate

[Major diastereoisomer (MAJ): Minor diastereoisomer (MIN) = 62:38]

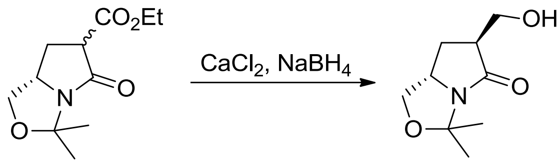


211 **281**

A flask charged with LHMDS (1M in toluene, 6.4 mL, 0.64 mmol) at −78 ºC was treated dropwise with a solution of lactam **211** (500 mg, 0.322 mmol) and diethyl carbonate (0.507 mL, 4.19 mmol) in THF (12 mL) over 30 mins. The reaction mixture was stirred for 1 h then warmed to 0 ºC and quenched with AcOH (0.92 mL). Et_2O (12 mL) was added and the mixture was concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 70% Et_2O in hexane) gave ester **281** (663 mg, 91%, 62:38 mixture of diastereoisomers) as a colourless oil: ν_{max}/cm^{-1} (film): 2984 (C-H), 2938 (C-H), 2873 (C-H), 1735 (C=O, ester), 1694 (C=O, amide); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (1.14H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3{}^{MIN}$), 1.31 (1.86H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3{}^{MAJ}$), 1.46 (1.86H, s, $C\underline{H}_3{}^{MAJ}$), 1.46 (1.14H, s, $C\underline{H}_3{}^{MIN}$), 1.65 (1.86H, s, $C\underline{H}_3{}^{MAJ}$), 1.66 (1.14H, s, $C\underline{H}_3{}^{MIN}$), 1.96 (0.38H, dt, *J* 13.0, 8.8 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 2.24 (0.62H, td, *J* 12.0, 8.7 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 2.36 (0.62H, ddd, *J* 12.6, 7.9, 6.2 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 2.49 (0.38H, ddd, *J* 13.0, 6.2, 0.8 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 3.45 (0.38H, t, *J* 8.8 Hz, 1 of $OC\underline{H}_2{}^{MIN}$), 3.55 (0.62H, t, *J* 8.7 Hz, 1 of $OC\underline{H}_2{}^{MAJ}$), 3.60 (0.38H, d, *J* 9.0 Hz, $C\underline{H}C{=}O^{MIN}$), 3.81 (0.62H, dd, *J* 11.7, 7.9 Hz, $C\underline{H}C{=}O^{MAJ}$), 4.07-4.14 (1H, m, 1 of $OC\underline{H}_2{}^{MAJ}$ and 1 of $OC\underline{H}_2{}^{MIN}$), 4.14-4.30 (2.62H, m, $C\underline{H}_2CH_3{}^{MAJ}$, $C\underline{H}_2CH_3{}^{MIN}$ and $OCH_2C\underline{H}^{MAJ}$), 4.47 (0.38H, ddd, *J* 8.9, 6.1, 2.6 Hz, $OCH_2C\underline{H}^{MIN}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2 ($CH_2\underline{C}H_3{}^{MIN}$), 14.3 ($CH_2\underline{C}H_3{}^{MAJ}$), 23.7 ($\underline{C}H_3{}^{MIN}$), 23.8 ($\underline{C}H_3{}^{MAJ}$), 26.7 ($\underline{C}H_3{}^{MIN}$), 26.8 ($\underline{C}H_3{}^{MAJ}$), 28.0 ($\underline{C}H_2CHC{=}O^{MAJ}$), 28.2 ($\underline{C}H_2CHC{=}O^{MIN}$), 54.2 ($\underline{C}HC{=}O^{MAJ}$), 55.3 ($\underline{C}HC{=}O^{MIN}$), 59.2 ($\underline{C}HN^{MAJ}$), 60.8 ($\underline{C}HN^{MIN}$), 61.8 ($\underline{C}H_2CH_3{}^{MAJ}$), 61.9 ($\underline{C}H_2CH_3{}^{MIN}$), 69.8 ($O\underline{C}H_2{}^{MAJ}$), 69.9 ($O\underline{C}H_2{}^{MIN}$), 91.8 ($\underline{C}(CH_3)_2{}^{MIN}$), 91.9 ($\underline{C}(CH_3)_2{}^{MAJ}$), 166.0 ($NC{=}O^{MIN}$), 166.4 ($NC{=}O^{MAJ}$), 169.5 ($CHC{=}O^{MAJ}$), 169.7

(CHC=O[MIN]); *m/z* (ES^+): 250 (MNa^+, 50%); HRMS (ES^+): $C_{11}H_{17}NO_4Na$ (MNa^+) requires: 250.1055; found 250.1055.

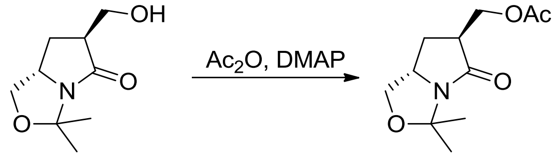
<u>282.</u> (6*S*,7a*S*)-6-(Hydroxymethyl)-3,3-dimethyltetrahydropyrrolo[1,2-*c*]oxazol-5-(3*H*)-one



281 **282**

A stirred solution of ester **281** (942 mg, 4.22 mmol) in MeOH (21 mL) at 0 ºC was treated with $CaCl_2$ (562 mg, 5.06 mmol) followed by $NaBH_4$ (192 mg, 5.06 mmol). The reaction was stirred for 1 h then treated with further $NaBH_4$ (160 mg, 4.22 mmol). After stirring for 2 h, the reaction mixture was diluted with H_2O (40 mL), brine (40 mL) and the organic material extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) then concentrated *in vacuo*. The solid was recrystallised from EtOAc, washed with cold Et_2O and dried to give alcohol **282** (600 mg, 76%) as a colourless solid: m.p. 107-108 ºC; $[\alpha]_D^{20}$ = +0.63, (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} ($CDCl_3$ cast): 3368 (br, O-H), 2990 (C-H), 2895 (C-H), 2897 (C-H), 1678 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (3H, s, $C\underline{H}_3$), 1.61-1.68 (4H, m, $C\underline{H}_3$ and 1 of $C\underline{H}_2$CHC=O), 2.22 (1H, ddd, *J* 12.2, 7.7, 6.0 Hz, 1 of $C\underline{H}_2$CHC=O), 3.01-3.12 (1H, br m, C<u>H</u>C=O), 3.46 (1H, t, *J* 8.8 Hz, 1 of $OC\underline{H}_2$), 3.70 (1H, ddd, *J* 11.0, 6.7, 3.8 Hz, 1 of $C\underline{H}_2OH$), 3.87 (1H, ddd, *J* 11.5, 7.3, 4.5 Hz, 1 of $C\underline{H}_2OH$), 4.11 (1H, dd, *J* 8.3, 5.6 Hz, 1 of $OC\underline{H}_2$), 4.20 (1H, tt, *J* 9.1, 5.7 Hz, $OCH_2C\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.0 ($\underline{C}H_3$), 26.8 ($\underline{C}H_3$), 27.4 ($\underline{C}H_2$CHC=O), 49.4 (<u>C</u>HC=O), 59.6 (<u>C</u>HN), 62.6 ($\underline{C}H_2OH$), 70.0 ($OC\underline{H}_2CH$), 91.5 ($\underline{C}(CH_3)_2$), 172.8 (<u>C</u>=O); *m/z* (CI): 186 (MH^+, 100%), 170 (10), 128 (35); HRMS (CI): $C_9H_{16}NO_3$ (MH^+) requires: 186.1130; found 186.1128.

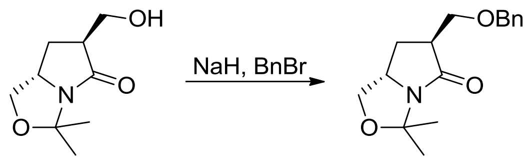
<u>283.</u> ((6*S*,7a*S*)-3,3-Dimethyl-5-oxohexahydropyrrolo[1,2-*c*]oxazol-6-yl)methyl acetate



282 **283**

A stirred solution of alcohol **282** (67 mg, 0.36 mmol) in CH_2Cl_2 (1.5 mL) was treated with Ac_2O (38 µL, 0.40 mmol) and DMAP (9.0 mg, 0.072 mmol). The reaction mixture was stirred for 3 d then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, Et_2O) gave acetate **283** (57 mg, 69%) as a colourless oil: $[\alpha]_D^{25}$= +64.0 (*c* 1.49, $CHCl_3$); ν_{max}/cm^{-1} ($CDCl_3$ cast): 2984 (C-H), 2938 (C-H), 2877 (C-H), 1738 (C=O, ester), 1689 (C=O, amide); ^1H NMR (600 MHz, $CDCl_3$) δ 1.47 (3H, s, $C\underline{H}_3$), 1.62-1.70 (4H, m, $C\underline{H}_3$ and 1 of $C\underline{H}_2CHC=O$), 2.05 (3H, s, $C\underline{H}_3C=O$), 2.33 (1H, ddd, *J* 12.5, 7.6, 6.6 Hz, 1 of $C\underline{H}_2CHC=O$), 3.11-3.18 (1H, m, $C\underline{H}C=O$), 3.44 (1H, t, *J* 8.7 Hz, 1 of $OC\underline{H}_2$), 4.12 (1H, dd, *J* 7.9, 5.6 Hz, 1 of $OC\underline{H}_2$), 4.16 (1H, tt, *J* 9.0, 6.0 Hz, $OCH_2C\underline{H}$), 4.29 (1H, dd, *J* 11.3, 5.3 Hz, 1 of $C\underline{H}_2OAc$), 4.33 (1H, dd, *J* 11.3, 4.1 Hz, 1 of $C\underline{H}_2OAc$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.0 ($\underline{C}H_3C=O$), 23.9 ($\underline{C}H_3$), 26.8 ($\underline{C}H_3$), 28.2 ($\underline{C}H_2CHC=O$), 47.3 ($\underline{C}HC=O$), 58.9 ($\underline{C}HN$), 63.2 ($\underline{C}H_2OAc$), 70.1 ($OC\underline{H}_2CH$), 91.8 ($\underline{C}(CH_3)_2$), 169.9 ($N\underline{C}=O$), 171.0 ($CH_3\underline{C}=O$); *m/z* (CI): 228 (MH^+, 100%), 212 ($MH^+–CH_4$, 44), 152 (17); HRMS (CI): $C_{11}H_{18}NO_4$ (MH^+) requires: 228.1236; found 228.1238.

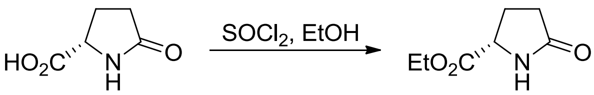
<u>284.</u> (6*S*,7a*S*)-6-((Benzyloxy)methyl)-3,3-dimethyltetrahydropyrrolo[1,2-*c*]oxazol-5(3*H*)-one



282 **284**

NaH (60% dispersion in oil, 93 mg, 2.31 mmol) was washed with hexanes to remove the oil then suspended in THF (2.5 mL) and cooled to 0 ºC was treated with a solution of alcohol **282** (297 mg, 1.60 mmol) in THF (2.5 mL) then stirred for 20 mins. The suspension was treated with BnBr (0.249 mL, 2.08 mmol) and the reaction was allowed to warm to room temperature and stirred for 14 h. The reaction mixture was quenched with H_2O (20 mL) and the organic material extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50% Et_2O in hexane) gave benzyl ether **284** (211 mg, 48%) as a colourless oil: $[\alpha]_D^{25}$ = +80.8 (*c* 1.13, $CHCl_3$); ν_{max}/cm^{-1} ($CDCl_3$ cast): 2983 (C-H), 2933 (C-H), 2866 (C-H), 1689 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 1.47 (3H, s, $C\underline{H}_3$), 1.64 (3H, s, $C\underline{H}_3$), 1.79 (1H, td, *J* 11.9, 8.7 Hz, 1 of $C\underline{H}_2CHC{=}O$), 2.33 (1H, ddd, *J* 12.3, 8.0, 6.4 Hz, 1 of $C\underline{H}_2CHC{=}O$), 3.08 (1H, dddd, *J* 11.4, 7.9, 5.9, 3.8 Hz, $C\underline{H}C{=}O$), 3.44 (1H, dd, *J* 8.3, 8.3 Hz, 1 of $OC\underline{H}_2$), 3.69 (1H, dd, *J* 9.4, 6.0 Hz, 1 of $C\underline{H}_2OBn$), 3.72 (1H, dd, *J* 9.4, 4.1 Hz, 1 of $C\underline{H}_2OBn$), 4.08 (1H, dd, *J* 8.3, 5.6 Hz, 1 of $OC\underline{H}_2$), 4.15 (1H, tt, *J* 8.8, 6.0 Hz, $C\underline{H}N$), 4.51 (1H, d, *J* 11.7 Hz, 1 of $C\underline{H}_2Ph$), 4.56 (1H, d, *J* 11.7 Hz, 1 of $C\underline{H}_2Ph$), 7.27-7.36 (5H, m, aromatic $C\underline{H}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.9 ($\underline{C}H_3$), 26.9 ($\underline{C}H_3$), 28.2 ($\underline{C}H_2CHC{=}O$), 48.7 ($\underline{C}HC{=}O$), 59.2 ($\underline{C}HN$), 69.4 ($\underline{C}H_2OBn$), 70.1 ($OC\underline{H}_2CH$), 73.4 ($C\underline{H}_2Ph$), 91.6 ($\underline{C}(CH_3)_2$), 127.7 (aromatic $\underline{C}H$), 127.7 (aromatic $\underline{C}H$), 128.5 (aromatic $\underline{C}H$), 138.4 (aromatic $\underline{C}$), 171.0 ($\underline{C}{=}O$); *m/z* (ES^+): 298 (MH^+, 100%), 276 (14); HRMS (ES^+): $C_{16}H_{21}NO_3Na$ (MH^+) requires: 298.1413; found 298.1419.

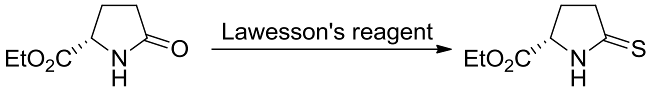
<u>285.</u> (*S*)-Ethyl 5-oxopyrrolidine-2-carboxylate[151]



285

A stirred solution of (*S*)-pyroglutamic acid (5.00 g, 38.7 mmol) in EtOH at –15 ºC was treated dropwise with $SOCl_2$ (5.6 mL, 38.7 mmol) then stirred for 100 mins. The reaction mixture was neutralised to pH 7 with saturated aq. $NaHCO_3$ solution and the organic material extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) then concentrated *in vacuo* to give lactam **285** (5.13 g, 84%) as a colourless solid: m.p. 46-47 ºC [lit.[151] = 46.5-47.5 ºC]; ν_{max}/cm^{-1} (solid): 3225 (br, N-H), 2981 (C-H), 2941 (C-H), 2908 (C-H), 1743 (C=O, ester), 1693 (C=O, amide); ^1H NMR (600 MHz, $CDCl_3$) δ 1.28 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 2.17-2.25 (1H, m, 1 of $C\underline{H}_2CHN$), 2.30-2.43 (2H, m, $C\underline{H}_2C{=}O$), 2.43-2.51 (1H, m, 1 of $C\underline{H}_2CHN$), 4.22 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CH_3$), 4.23-4.25 (1H, m, $C\underline{H}N$), 6.41 (1H, br s, $N\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3 ($CH_2\underline{C}H_3$), 24.9 ($\underline{C}H_2CHN$), 29.3 ($\underline{C}H_2C{=}O$), 55.5 ($\underline{C}HN$), 61.8 ($\underline{C}H_2CH_3$), 172.1 ($O\underline{C}{=}O$), 178.0 ($N\underline{C}{=}O$).

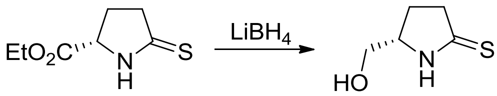
286. (*S*)-Ethyl 5-thioxopyrrolidine-2-carboxylate



285 **286**

Prepared by the method of Busqué.[127] A stirred solution of lactam **285** (2.00 g, 12.7 mmol) in THF (30 mL) was treated with Lawesson's reagent (2.6 g, 6.33 mmol) then stirred for 2 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 40% EtOAc in hexane) gave a solid. Re-purification by flash chromatography (SiO_2, 65% Et_2O in hexane) which gave thiolactam **286** (1.8 g, 82%) as a colourless solid: m.p. 37-38 ºC [lit.[127] = 35-36 ºC]; ν_{max}/cm^{-1} (solid): 3300 (br, N-H), 2982 (C-H), 2941 (C-H), 2875 (C-H), 1743 (C=O), 1716, 1524 (C=S); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 2.31-2.39 (1H, m, 1 of $C\underline{H}_2CHN$), 2.52-2.60 (1H, m, 1 of $C\underline{H}_2CHN$), 2.89-3.03 (2H, m, $C\underline{H}_2C{=}S$), 4.20-4.29 (2H, m, $C\underline{H}_2CH_3$), 4.51 (1H, dd, *J* 8.7, 6.4 Hz, $C\underline{H}N$), 8.10 (1H, br s, $N\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2 ($CH_2\underline{C}H_3$), 27.2 ($\underline{C}H_2CHN$), 42.7 ($\underline{C}H_2C{=}S$), 62.3 ($\underline{C}H_2CH_3$), 62.6 ($\underline{C}HN$), 170.1 ($\underline{C}{=}O$), 206.8 ($\underline{C}{=}S$).

287. (*S*)-5-(Hydroxymethyl)pyrrolidine-2-thione[127]

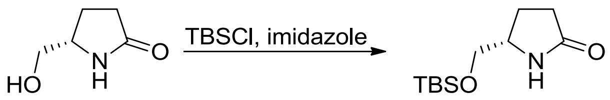


286 **287**

A stirred solution of ester **286** (11.1 g, 64.1 mmol) in THF (100 mL) was treated with $LiBH_4$ (1.5 g, 70.5 mmol) then stirred for 1 h. The reaction mixture was cooled to 0 ºC and treated with 20% aqueous acetic acid (40 mL) then adsorbed onto silica gel. Purification by flash chromatography (SiO_2, 6% MeOH in $CHCl_3$) gave alcohol **287** (7.43 g, 88%) as a colourless solid: m.p. 125-126 ºC [lit.[127] = 124-125 ºC]; ν_{max}/cm^{-1} (solid): 3178 (br, O-H), 3046 (br, N-H), 2973 (C-H), 2932 (C-H), 2877 (C-H), 1532 (C=S); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.85 (1H, dddd, *J* 17.7, 11.3, 6.0, 5.3 Hz, 1 of $C\underline{H}_2CH_2C{=}S$), 2.09 (1H, m, 1 of $C\underline{H}_2CH_2C{=}S$), 2.65 (1H, ddd, *J* 17.8, 9.8, 6.4 Hz, 1 of $C\underline{H}_2C{=}S$), 2.73 (1H, ddd, *J* 17.7, 9.8, 6.4 Hz, 1 of $C\underline{H}_2C{=}S$), 3.37-3.44 (2H, m, $C\underline{H}_2OH$), 3.84 (1H, sxt, *J* 4.5 Hz, $C\underline{H}N$), 4.91 (1H, t, *J* 5.5 Hz, $CH_2O\underline{H}$), 10.12 (1H, br s, $N\underline{H}$); ^{13}C

NMR (150 MHz, DMSO-d_6) δ 24.7 (C̲H$_2$CH$_2$C=S), 43.2 (C̲H$_2$C=S), 62.7 (C̲H$_2$OH), 63.6 (C̲HN), 203.7 (C̲=S).

288. (*S*)-5-(*tert*-Butyldimethylsilanyloxymethyl)pyrrolidin-2-one

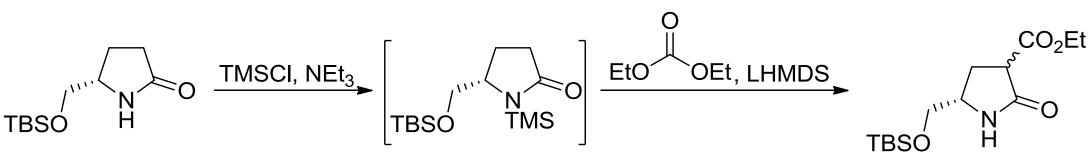


203 **288**

Prepared by the method of Hsung.[128] A flask was charged with alcohol **203** (552 mg, 4.79 mmol) and TBSCl (867 mg, 5.75 mmol) which were then dissolved in CH_2Cl_2 (6 mL). The solution was treated with imidazole (489 mg, 7.19 mmol) then stirred for 2 h. The mixture was washed with H_2O (10 mL), dried ($MgSO_4$) then concentrated *in vacuo* to give lactam **288** (1.02, 93%) as an oil which was used without further purification: ν_{max}/cm^{-1} (film): 3223 (br, N-H), 2953 (C-H), 2929 (C-H), 2857 (C-H), 1694 (C=O); ^{1}H NMR (600 MHz, CDCl$_3$) δ 0.05 (6H, s, 2 × SiCH̲$_3$), 0.88 (9H, s, C(CH̲$_3$)$_3$), 1.73 (1H, dddd, *J* 13.0, 9.8, 7.3, 5.5 Hz, 1 of CH̲$_2$CH$_2$C=O), 2.18 (1H, dddd, *J* 13.0, 8.9, 8.0, 6.9 Hz, 1 of CH̲$_2$CH$_2$C=O), 2.29-2.39 (2H, m, CH̲$_2$C=O), 3.43 (1H, dd, *J* 10.0, 7.9 Hz, 1 of OCH̲$_2$), 3.62 (1H, dd, *J* 10.0, 3.8 Hz, 1 of OCH̲$_2$), 3.72-3.77 (1H, m, CH̲N), 5.80 (1H, br s, NH); ^{13}C NMR (150 MHz, CDCl$_3$) δ −5.33 (SiC̲H$_3$), −5.31 (SiC̲H$_3$), 18.3 (SiC̲(CH$_3$)$_3$), 22.8 (C̲H$_2$CH$_2$C=O), 25.9 (SiC(C̲H$_3$)$_3$), 29.9 (C̲H$_2$C=O), 55.9 (C̲HN), 67.1 (OC̲H$_2$), 177.8 (C̲=O).

289. (5*S*)-Ethyl 5-(*tert*-butyldimethylsilanyloxymethyl)-2-oxopyrrolidine-3-carboxylate

[Major diastereoisomer (MAJ): Minor diastereoisomer (MIN) = 70:30]

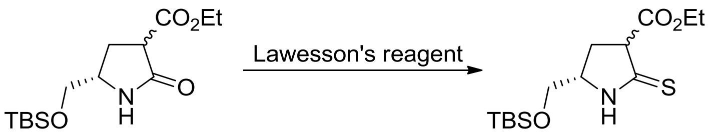


288 **328** **289**

A stirred solution of lactam **288** (194 mg, 0.846 mmol) in CH_2Cl_2 (5 mL) was treated with NEt_3 (0.248 mL, 1.78 mmol) then TMSCl (0.215 mL, 1.69 mmol). The reaction mixture was stirred for 30 mins then concentrated *in vacuo* to give a residue which was suspended in Et_2O then filtered. The filtrate was concentrated *in vacuo* to give lactam **328** as a pale red oil. Diethyl carbonate (0.133 mL, 1.10 mmol) and lactam **328** were dissolved in THF (3 mL) and added over 20 mins to LHMDS (1 M in THF, 1.69 mL, 1.69 mmol) at −78 ºC. The reaction mixture was stirred for 1 h, warmed to 0 ºC over 30 mins then quenched with saturated aq. NH_4Cl solution (5 mL). The mixture was diluted with H_2O (5 mL) and the organic material extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50% to 75% Et_2O in hexane) gave lactam **289** (173 mg, 68%) as a yellow oil: ν_{max}/cm^{-1} (film): 3221 (br, N-H), 2955 (C-H), 2930 (C-H), 2857 (C-H), 1737 (C=O), 1702 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 0.05 (4.2H, s, 2 × $SiC\underline{H}_3^{MAJ}$), 0.06 (1.8H, s, 2 × $SiC\underline{H}_3^{MIN}$), 0.88 (9H, s, $C(C\underline{H}_3)_3^{MAJ}$ and $C(C\underline{H}_3)_3^{MIN}$), 1.30 (2.1H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3^{MAJ}$), 1.31 (0.9H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3^{MIN}$), 2.00 (0.7H, ddd, *J* 13.9, 9.8, 4.5 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 2.10 (0.3H, ddd, *J* 13.6, 7.9, 6.8 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 2.37 (0.3H, ddd, *J* 13.6, 9.8, 7.5 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 2.56 (0.7H, ddd, *J* 13.6, 8.3, 6.4 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 3.40-3.48 (1.7H, m, $C\underline{H}C{=}O^{MAJ}$, $C\underline{H}C{=}O^{MIN}$ and 1 of $OC\underline{H}_2^{MAJ}$), 3.53 (0.3H, t, *J* 9.4 Hz, 1 of $OC\underline{H}_2^{MIN}$), 3.64 (0.7H, dd, *J* 10.2, 3.8 Hz, 1 of $OC\underline{H}_2^{MAJ}$), 3.69 (0.3H, dd, *J* 9.8, 4.1 Hz, 1 of $OC\underline{H}_2^{MIN}$), 3.72-3.78 (0.3H, m, $C\underline{H}N^{MIN}$), 3.83-3.89 (0.7H, m, $C\underline{H}N^{MAJ}$), 4.20-4.27 (2H, m, $C\underline{H}_2CH_3^{MAJ}$ and $C\underline{H}_2CH_3^{MIN}$), 5.95 (0.7H, s, $N\underline{H}^{MAJ}$), 6.02 (0.3H, s, $N\underline{H}^{MIN}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.4 ($Si\underline{C}H_3^{MIN}$), −5.323 ($Si\underline{C}H_3^{MAJ}$), −5.315 ($Si\underline{C}H_3^{MAJ}$), −5.30 ($Si\underline{C}H_3^{MIN}$), 14.3 ($CH_2\underline{C}H_3^{MAJ}$ and $CH_2\underline{C}H_3^{MIN}$), 18.30 ($Si\underline{C}(CH_3)_3^{MIN}$), 18.31 ($Si\underline{C}(CH_3)_3^{MAJ}$), 25.9 ($SiC(\underline{C}H_3)_3^{MAJ}$ and $SiC(\underline{C}H_3)_3^{MIN}$), 26.5 ($\underline{C}H_2CHC{=}O^{MIN}$), 27.2 ($\underline{C}H_2CHC{=}O^{MAJ}$), 47.7 ($\underline{C}HC{=}O^{MAJ}$), 47.8 ($\underline{C}HC{=}O^{MIN}$), 54.3 ($\underline{C}HN^{MIN}$), 54.4 ($\underline{C}HN^{MAJ}$), 61.89 ($\underline{C}H_2CH_3^{MAJ}$), 61.92 ($\underline{C}H_2CH_3^{MIN}$), 66.7 ($O\underline{C}H_2^{MAJ}$), 67.1 ($O\underline{C}H_2^{MIN}$), 170.0 ($\underline{C}{=}O^{MIN}$), 170.2 ($\underline{C}{=}O^{MAJ}$), 172.1 ($N\underline{C}{=}O^{MIN}$), 172.5 ($N\underline{C}{=}O^{MAJ}$); *m/z* ($ES^+$): 324 ($MH^+$, 100%), 302 (20), 256 (45); HRMS (ES^+): $C_{14}H_{27}NO_4SiNa$ (MH^+) requires: 324.1607; found 324.1597.

290. (5*S*)-Ethyl 5-(*tert*-butyldimethylsilanyloxymethyl)-2-thioxopyrrolidine-3-carboxylate

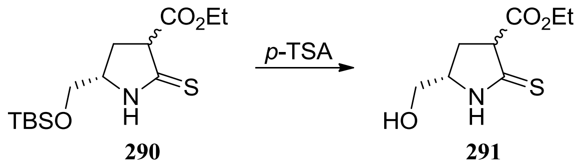
[Major diastereoisomer (MAJ): Minor diastereoisomer (MIN) = 57:43]



289 **290**

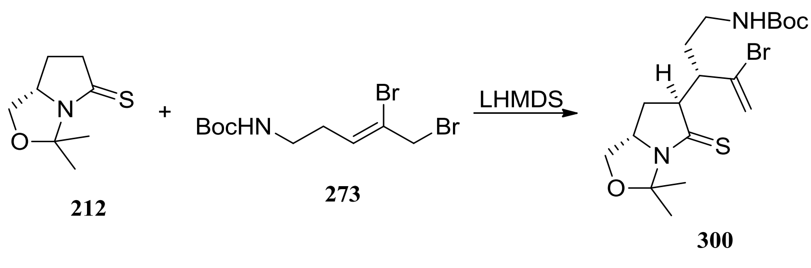
A stirred solution of lactam **289** (753 mg, 2.50 mmol) in THF (25 mL) was treated with Lawesson's reagent (556 mg, 1.37 mmol) then heated to 60 ºC for 15 mins. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 30% Et_2O in hexane) gave thiolactam **290** (668 mg, 84%) as a colourless solid: m.p. 68-69 ºC; ν_{max}/cm^{-1} ($CDCl_3$ cast): 3162 (br, N-H), 2954 (C-H), 2929 (C-H), 2857 (C-H), 1735 (C=O), 1517 (C=S); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.07 (3.42H, s, 2 × $SiC\underline{H}_3{}^{MAJ}$), 0.074 (1.29H, s, 1 of $SiC\underline{H}_3{}^{MIN}$), 0.08 (1.29H, s, 1 of $SiC\underline{H}_3{}^{MIN}$), 0.889 (5.13H, s, $C(C\underline{H}_3)_3{}^{MAJ}$), 0.895 (3.87H, s, $C(C\underline{H}_3)_3{}^{MIN}$), 1.31 (1.71H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3{}^{MAJ}$), 1.33 (1.29H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3{}^{MIN}$), 2.07 (0.57H, ddd, *J* 13.6, 9.4, 6.4 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 2.16 (0.43H, dt, *J* 13.6, 7.2 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 2.49 (0.43H, ddd, *J* 13.6, 9.4, 7.9 Hz, 1 of $C\underline{H}_2CHC{=}O^{MIN}$), 2.56 (0.57H, ddd, *J* 13.2, 7.9, 4.9 Hz, 1 of $C\underline{H}_2CHC{=}O^{MAJ}$), 3.50 (0.57H, dd, *J* 10.4, 7.7 Hz, 1 of $OC\underline{H}_2{}^{MAJ}$), 3.66 (0.43H, t, *J* 9.4 Hz, 1 of $OC\underline{H}_2{}^{MIN}$), 3.70-3.76 (1H, m, 1 of $OC\underline{H}_2{}^{MAJ}$ and 1 of $OC\underline{H}_2{}^{MIN}$), 3.81-3.89 (1H, m, $C\underline{H}C{=}S^{MAJ}$ and $C\underline{H}C{=}S^{MIN}$), 3.98-4.05 (0.43H, m, $C\underline{H}N^{MIN}$), 4.15-4.21 (0.57H, m, $C\underline{H}N^{MAJ}$), 4.21-4.33 (2H, m, $C\underline{H}_2CH_3{}^{MAJ}$ and $C\underline{H}_2CH_3{}^{MIN}$) 7.92 (0.57H, br s, $N\underline{H}^{MAJ}$), 7.98 (0.43H, br s, $N\underline{H}^{MIN}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.35 ($Si\underline{C}H_3{}^{MAJ}$), −5.33 ($Si\underline{C}H_3{}^{MIN}$), −5.31 ($Si\underline{C}H_3{}^{MAJ}$), −5.26 ($Si\underline{C}H_3{}^{MIN}$), 14.25 ($CH_2\underline{C}H_3{}^{MAJ}$), 14.28 ($CH_2\underline{C}H_3{}^{MIN}$), 18.32 ($Si\underline{C}(CH_3)_3{}^{MAJ}$), 18.33 ($Si\underline{C}(CH_3)_3{}^{MIN}$), 25.93 ($SiC(\underline{C}H_3)_3{}^{MAJ}$), 25.94 ($SiC(\underline{C}H_3)_3{}^{MIN}$), 28.8 ($\underline{C}H_2CHC{=}O^{MIN}$), 29.6 ($\underline{C}H_2CHC{=}O^{MAJ}$), 58.7 ($\underline{C}HC{=}S^{MIN}$), 59.0 ($\underline{C}HC{=}S^{MAJ}$), 62.02 ($\underline{C}H_2CH_3{}^{MAJ}$), 62.05 ($\underline{C}H_2CH_3{}^{MIN}$), 62.7 ($\underline{C}HN^{MIN}$), 63.0 ($\underline{C}HN^{MAJ}$), 65.7 ($O\underline{C}H_2{}^{MAJ}$), 66.0 ($O\underline{C}H_2{}^{MIN}$), 170.05 ($\underline{C}{=}O^{MIN}$), 170.14 ($\underline{C}{=}O^{MAJ}$), 200.4 ($\underline{C}{=}S^{MIN}$), 200.5 ($\underline{C}{=}S^{MAJ}$); *m/z* ($ES^-$): 316 ($(M{-}H)^-$, 100%); HRMS ($ES^-$): $C_{14}H_{26}NO_3SSi$ $(M{-}H)^-$ requires: 316.1403; found 316.1395.

291. (5*S*)-Ethyl 5-(hydroxymethyl)-2-thioxopyrrolidine-3-carboxylate



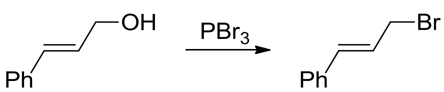
A stirred solution of silyl ether **290** (146 mg, 0.460 mmol) in MeOH (5 mL) was treated with *p*-TSA (26 mg, 0.14 mmol). The mixture was stirred for 18 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50% Et_2O in hexane to 100% Et_2O) gave alcohol **291** (93 mg, 99%, 12:1 ratio of diastereoisomers) as a colourless solid: m.p. 68-69 ºC; ν_{max}/cm^{-1} (solid): 3405 (br, O-H), 3192 (br, N-H), 2987 (C-H), 2927 (C-H), 2877 (C-H), 1726 (C=O), 1520 (C=S); ^{1}H NMR (600 MHz, $CDCl_3$, for major diastereoisomer only) δ 1.33 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 2.25-2.34 (1H, m, 1 of $C\underline{H}_2$CHC=O), 2.53 (1H, ddd, *J* 13.2, 9.0, 7.9 Hz, 1 of $C\underline{H}_2$CHC=O), 3.12 (1H, br s, O<u>H</u>), 3.64-3.74 (1H, m, 1 of $OC\underline{H}_2$), 3.79-3.95 (2H, m, 1 of $OC\underline{H}_2$ and C<u>H</u>C=S), 4.04-4.17 (1H, m, C<u>H</u>N), 4.19-4.34 (2H, m, $C\underline{H}_2CH_3$), 9.03 (1H, br s, N<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$, for major diastereoisomer only) δ 14.2 ($CH_2\underline{C}H_3$), 28.7 ($\underline{C}H_2$CHC=O), 58.7 (<u>C</u>HC=S), 62.4 ($\underline{C}H_2CH_3$), 62.8 (<u>C</u>HN), 64.1 ($O\underline{C}H_2$), 171.2 (<u>C</u>=O), 200.6 (<u>C</u>=S); *m/z* (CI): 204 (MH^+, 100%), 132 ($MH^+–CH_2CH_2O_2C$, 100); HRMS (CI): $C_8H_{14}NO_3S$ (MH^+) requires: 204.0694; found 204.0701.

300. *tert*-Butyl ((*S*)-4-bromo-3-((6*S*,7a*S*)-3,3-dimethyl-5-thioxohexahydropyrrolo[1,2-*c*]oxazol-6-yl)pent-4-en-1-yl)carbamate



A stirred solution of HMDS (0.10 mL, 0.49 mmol) in THF (1 mL) at 0 ºC was treated with *n*-butyllithium (2.5 M in hexanes, 0.25 mL, 0.47 mmol) then stirred for 15 mins. The solution was treated with thioamide **212** (38 mg, 0.22 mmol) in THF (0.5 mL) and warmed to room temperature then stirred for 30 mins. The reaction mixture was treated with allyl bromide **273** (84 mg, 0.25 mmol) in THF (0.5 mL) and stirred for 45 mins. The reaction was quenched with 1M NaOH solution (5 mL), the mixture was diluted with Et_2O (10 mL) and the layers were separated. The organic layer was washed with H_2O (5 mL), brine (5 mL), dried over K_2CO_3 then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 40% Et_2O in hexane) gave thiolactam **300** (40 mg, 41%, 80% diastereomeric excess) as a colourless oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 3362 (br, N-H), 2979 (C-H), 2933 (C-H), 2869 (C-H), 1701 (C=O); ^1H NMR (600 MHz, $CDCl_3$, data for major diastereoisomer only) δ 1.43 (9H, s, $C(C\underline{H}_3)_3$), 1.54-1.61 (1H, m, 1 of $NHCH_2C\underline{H}_2$), 1.65 (3H, s, $C\underline{H}_3$), 1.84 (3H, s, $C\underline{H}_3$), 1.86-1.97 (2H, m, 1 of $C\underline{H}_2CHC{=}S$ and 1 of $NHCH_2C\underline{H}_2$), 2.27 (1H, dd, *J* 12.8, 6.8 Hz, 1 of $C\underline{H}_2CHC{=}S$), 2.92-3.04 (1H, m, 1 of $NHC\underline{H}_2$), 3.15 (1H, br dt, *J* 10.9, 3.4 Hz, $C\underline{H}C{=}CH_2$), 3.23-3.34 (1H, m, 1 of $NHC\underline{H}_2$), 3.45 (1H, dd, *J* 9.8, 8.7 Hz, 1 of $OC\underline{H}_2$), 3.67 (1H, br d, *J* 9.8 Hz, $C\underline{H}C{=}S$), 4.08 (1H, dd, *J* 8.3, 5.6 Hz, 1 of $OC\underline{H}_2$), 4.37-4.49 (1H, m, $C\underline{H}N$), 4.65 (1H, br s, $N\underline{H}$), 5.66 (1H, d, *J* 2.3 Hz, 1 of $C{=}C\underline{H}_2$), 5.89 (1H, br s, 1 of $C{=}C\underline{H}_2$); ^{13}C NMR (150 MHz, $CDCl_3$, data for major diastereoisomer only) δ 22.1 ($\underline{C}H_3$), 25.1 ($\underline{C}H_3$), 25.8 ($C\underline{H}_2CHC{=}S$), 28.5 ($C(\underline{C}H_3)_3$), 28.6 ($NHCH_2\underline{C}H_2$), 38.6 ($NH\underline{C}H_2CH_2$), 50.6 ($\underline{C}HC{=}CH_2$), 66.0 ($\underline{C}HC{=}S$), 68.8 ($O\underline{C}H_2$), 69.0 ($\underline{C}HN$), 79.4 ($\underline{C}(CH_3)_3$), 93.8 ($\underline{C}(CH_3)_2$), 119.4 ($C{=}\underline{C}H_2$), 135.2 ($\underline{C}{=}CH_2$), 156.0 ($\underline{C}{=}O$), 197.0 ($\underline{C}{=}S$); *m/z* (CI): 433/435 (MH^+, 52/53%), 393/395 (74/75), 353 ($MH^+{-}HBr$, 100), 172 (31); HRMS (CI): $C_{18}H_{30}{}^{79}BrN_2O_3S$ (MH^+) requires: 433.1161; found 433.1158.

<u>301.</u> (*E*)-(3-Bromoprop-1-en-1-yl)benzene[135]

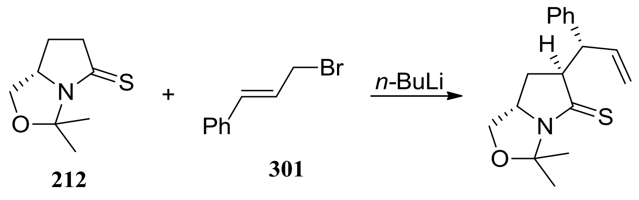


301

A stirred solution of cinnamyl alcohol (2.17 g, 16.2 mmol) in THF (25 mL) was cooled to 0 ºC and treated with PBr_3 (0.608 mL, 6.47 mmol). The reaction mixture was stirred for 1 h and then quenched with saturated aq. $NaHCO_3$ solution (25 mL). The mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were washed with H_2O (25 mL), brine (25 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 2% Et_2O in hexane) gave bromide **301** (1.72 g, 56%) as a pale yellow solid: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 3059 (C-H), 3029 (C-H), 2959 (C-H); ^1H NMR (600 MHz, $CDCl_3$) δ 4.17 (2H, dd, *J* 7.9, 0.8 Hz, $C\underline{H}_2Br$), 6.40 (1H, dt, *J* 15.5, 7.9

Hz, PhCH=C<u>H</u>), 6.65 (1H, d, *J* 15.4 Hz, PhC<u>H</u>=CH), 7.26-7.41 (5H, m, aromatic C<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.6 (<u>C</u>H_2Br), 125.3 (PhCH=<u>C</u>H), 126.9 (aromatic <u>C</u>H), 128.5 (aromatic <u>C</u>H), 128.8 (aromatic <u>C</u>H), 134.7 (Ph<u>C</u>H=CH), 135.9 (aromatic <u>C</u>).

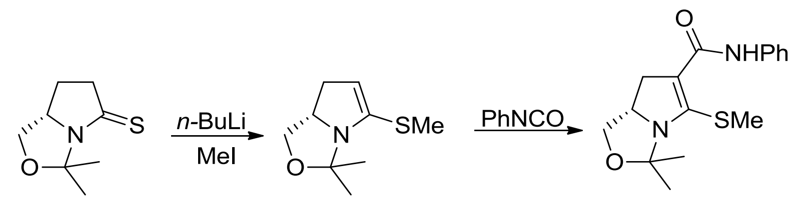
<u>303.</u> (6*S*,7a*S*)-3,3-dimethyl-6-((*R*)-1-phenylallyl)tetrahydropyrrolo[1,2-*c*]oxazole-5-(3*H*)-thione



212 **301** **303**

A stirred solution of thioamide **212** (205 mg, 1.20 mmol) in THF (5 mL) at 0 ºC was treated with *n*-butyllithium (2.5 M in hexane, 0.55 mL, 1.3 mmol) then stirred for 15 mins. The reaction mixture was treated with allyl bromide **301** (260 mg, 1.32 mmol) in THF (1 mL) and stirred for 30 mins at 0 ºC and 1 h at room temperature. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (6 mL) and the organic material extracted with Et_2O (3 × 6 mL). The combined organic extracts were washed with brine (6 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 20% Et_2O in hexane) gave thioamide **303** (252 mg, 73%, 92% diastereomeric excess) as a colourless solid: m.p. 119-120 ºC; $[\alpha]_D^{20}$ = –94.3 (*c* 0.35, $CHCl_3$); ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2984 (C-H), 2928 (C-H), 2869 (C-H), 1484 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$, data for major diastereoisomer only) δ 1.40 (3H, s, C<u>H</u>$_3$), 1.80 (3H, s, C<u>H</u>$_3$), 1.90 (1H, dt, *J* 12.6, 9.7 Hz, 1 of C<u>H</u>$_2$CHC=S), 2.09 (1H, dd, *J* 12.8, 6.4 Hz, 1 of C<u>H</u>$_2$CHC=S), 2.82 (1H, tt, *J* 10.2, 6.0 Hz, C<u>H</u>N), 3.25 (1H, dd, *J* 10.4, 8.5 Hz, 1 of OC<u>H</u>$_2$), 3.73 (1H, dd, *J* 8.3, 5.6 Hz, 1 of OC<u>H</u>$_2$), 3.78 (1H, dd, *J* 9.2, 3.2 Hz, CH_2=CHC<u>H</u>), 4.33-4.36 (1H, m, C<u>H</u>C=S), 5.15 (1H, dq, *J* 17.4, 1.0 Hz, CH=C<u>H</u>$_2^{trans}$), 5.28 (1H, dt, *J* 10.5, 1.3 Hz, CH=C<u>H</u>$_2^{cis}$), 6.20 (1H, ddd, *J* 17.5, 10.7, 5.6 Hz, C<u>H</u>=CH_2), 7.26-7.38 (5H, m, aromatic C<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$, data for major diastereoisomer only) δ 22.3 (<u>C</u>H_3), 24.3 (<u>C</u>H_3), 26.4 (<u>C</u>H_2CHC=S), 50.1 (<u>C</u>HC=S), 66.8 (CH_2=CH<u>C</u>H), 68.3 (O<u>C</u>H_2), 68.4 (<u>C</u>HN), 93.2 (<u>C</u>$(CH_3)_2$), 115.6 (<u>C</u>H_2=CH), 127.7 (aromatic <u>C</u>H), 128.4 (aromatic <u>C</u>H), 128.9 (aromatic <u>C</u>H), 138.8 (CH_2=<u>C</u>H), 139.5 (aromatic <u>C</u>), 197.6 (<u>C</u>=S); *m/z* (EI): 287 (M^+, 23%), 117 (PhCHCH=CH_2^+, 17), 86 (100); HRMS (EI): $C_{17}H_{21}NOS$ (M^+) requires: 287.1339; found 287.1341.

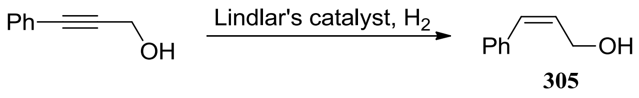
<u>304.</u> (*S*)-3,3-Dimethyl-5-(methylsulfanyl)-*N*-phenyl-1,3,7,7a-tetrahydropyrrolo[1,2-*c*]oxazole-6-carboxamide



212 **329** **304**

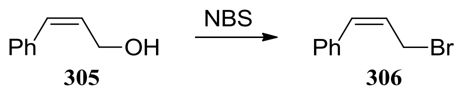
A stirred solution of thioamide **212** (150 mg, 0.876 mmol) in THF (5 mL) at 0 ºC was treated with *n*-butyllithium (2.5 M in hexanes, 0.39 mL, 0.96 mmol). The reaction mixture was stirred for 10 mins, cooled to −78 ºC then treated with MeI (0.082 mL, 1.3 mmol). The reaction mixture was warmed to room temperature and stirred for 15 mins. The reaction mixture was quenched with H_2O (5 mL) and the organic material extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) then concentrated *in vacuo* to give *N*,*S*-ketene acetal **329** as a yellow oil which was dissolved in THF (0.5 mL). The solution was treated with PhNCO (0.096 mL, 0.88 mmol) then stirred for 2 h. The reaction mixture was concentrated *in vacuo* to give secondary amide **304** (158 mg, 59%) as a pale yellow oil: $[\alpha]_D^{20}$ = +491.7 (*c* 0.24, $CHCl_3$); ν_{max}/cm^{-1} (film): 3300 (N-H), 2986 (C-H), 2930 (C-H), 2870 (C-H), 1644 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 1.56 (3H, s, C<u>H</u>$_3$), 1.58 (3H, s, C<u>H</u>$_3$), 2.48 (3H, s, SC<u>H</u>$_3$), 2.87 (1H, dd, *J* 16.3, 8.7 Hz, 1 of C<u>H</u>$_2$C=C), 2.96 (1H, dd, *J* 16.6, 11.3 Hz, 1 of C<u>H</u>$_2$C=C), 3.68 (1H, t, *J* 8.5 Hz, 1 of OC<u>H</u>$_2$), 4.22 (1H, dd, *J* 8.8, 7.0 Hz, 1 of OC<u>H</u>$_2$), 4.29-4.38 (1H, m, C<u>H</u>N), 7.05-7.10 (1H, m, aromatic C<u>H</u>), 7.29-7.34 (2H, m, aromatic C<u>H</u>), 7.56-7.62 (2H, m, aromatic C<u>H</u>), 9.51 (1H, br s, N<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.5 (S<u>C</u>H$_3$), 24.0 (<u>C</u>H$_3$), 28.7 (<u>C</u>H$_3$), 35.0 (<u>C</u>H$_2$C=C), 61.9 (<u>C</u>HN), 69.9 (O<u>C</u>H$_2$), 96.1 (<u>C</u>(CH$_3$)$_2$), 119.6 (aromatic <u>C</u>H), 120.6 (<u>C</u>=CS), 123.7 (aromatic <u>C</u>H), 129.1 (aromatic <u>C</u>H), 138.6 (aromatic <u>C</u>), 145.6 (C=<u>C</u>S), 163.0 (<u>C</u>=O); *m/z* (CI): 304 (MH^+, 4%), 212 (MH^+–NHPh, 6), 84 (100); HRMS (CI): $C_{24}H_{27}N_2O_2S$ (MH^+) requires: 407.1793; found 407.1796.

305. (*Z*)-3-Phenylprop-2-en-1-ol



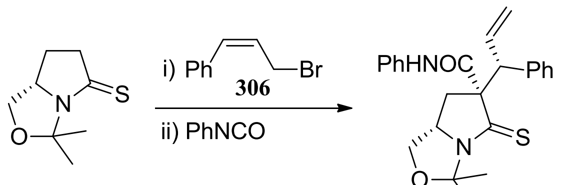
Prepared by the method of Pelter.[139] A stirred solution of phenyl propargyl alcohol (580 mg, 4.39 mmol) in MeOH (8 mL) was degassed (3 × freeze-pump-thaw) then treated with Lindlar's catalyst (3.5wt % on carbon, 98 mg, 0.032 mmol). The reaction flask was evacuated and filled with H_2. After stirring for 6.5 h, the H_2 atmosphere was evacuated and replaced with argon. The reaction mixture was filtered through Celite® and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 25-50% Et_2O in hexane) gave allylic alcohol **305**, (529 mg, 90%, 11:1 ratio of *Z*:*E* isomers) as a yellow oil; ν_{max}/cm^{-1} (film): 3319 (br, O-H), 2867 (C-H); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.45 (2H, dd, *J* 6.4, 1.5 Hz, $C\underline{H}_2OH$), 5.88 (1H, dt, *J* 11.7, 6.4 Hz, $PhCH{=}C\underline{H}$), 6.58 (1H, d, *J* 12.0 Hz, $PhC\underline{H}{=}CH$), 7.19-7.37 (5H, m, aromatic $C\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 59.8 ($\underline{C}H_2OH$), 127.4 (aromatic $\underline{C}H$), 128.4 (aromatic $\underline{C}H$), 128.9 (aromatic $\underline{C}H$), 131.18 ($Ph\underline{C}H{=}CH$), 131.22 ($PhCH{=}\underline{C}H$), 136.6 (aromatic $\underline{C}$).

306. (*Z*)-(3-Bromoprop-1-en-1-yl)benzene[140]



A stirred solution of alcohol **305** (211 mg, 1.57 mmol) in CH_2Cl_2 (5 mL) at 0 ºC was treated with PPh_3 (454 mg, 1.73 mmol) and NBS (308 mg, 1.73 mmol) then warmed to room temperature. The reaction mixture was stirred for 3 h and then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, hexane) gave bromide **306**, (213 mg, 69%) as a colourless oil; ν_{max}/cm^{-1} ($CDCl_3$ cast): 3057 (C-H), 3025 (C-H), 2928 (C-H); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.17 (2H, d, *J* 8.7 Hz, $C\underline{H}_2Br$), 5.99 (1H, dt, *J* 11.2, 8.7 Hz, $PhCH{=}C\underline{H}$), 6.61 (1H, d, *J* 11.3 Hz, $PhC\underline{H}{=}CH$), 7.26-7.42 (5H, m, aromatic $C\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.1 ($C\underline{H}_2Br$), 127.1 ($PhCH{=}\underline{C}H$), 127.8 (aromatic $\underline{C}H$), 128.7 (aromatic $\underline{C}H$), 128.8 (aromatic $\underline{C}H$), 133.6 ($Ph\underline{C}H{=}CH$), 135.7 (aromatic $\underline{C}$).

<u>308.</u> (6*S*,7a*S*)-3,3-Dimethyl-*N*-phenyl-6-((*R*)-1-phenylallyl)-5-thioxohexahydro pyrrolo[1,2-*c*]oxazole-6-carboxamide



[Method A]

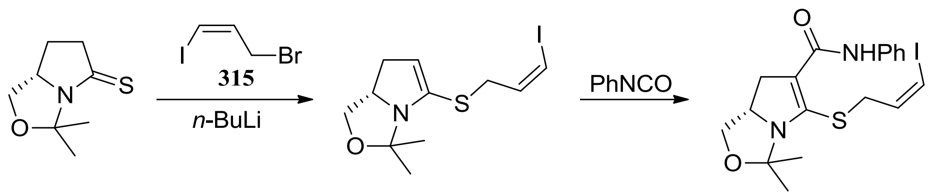
A stirred solution of thioamide **212** (87 mg, 0.51 mmol) in THF (1 mL) at 0 ºC was treated dropwise with *n*-butyllithium (2.02 M in hexanes, 0.26 mL, 0.54 mmol) then stirred for 15 mins. The reaction mixture was cooled to –78 ºC then treated dropwise with bromide **306** (111 mg, 0.56 mmol) in THF (1 mL). The reaction mixture was stirred for 10 mins and then warmed to room temperature over 20 mins. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (1 mL), brine (2 mL) and the organic material extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried (hydrophobic frit) then concentrated *in vacuo* to give an oil which was dissolved in THF (1 mL) then treated with phenyl isocyanate (0.084 mL, 0.77 mmol). The reaction mixture was stirred for 21 h then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 15% EtOAc in hexane) gave thioamide **308**, (101 mg, 49%, 92% diastereoisomeric excess) as a yellow viscous oil.

[Method B]

A stirred solution of thioamide **212** (141 mg, 0.824 mmol) in THF (2 mL) at 0 ºC was treated with *n*-butyllithium (2.02 M in hexanes, 0.4 mL, 0.81 mmol) then stirred for 25 mins. The reaction mixture was cooled to –78 ºC then treated with allylic bromide **307** (195 mg, 0.989 mmol) in THF (2 mL). The reaction mixture was stirred for 15 mins then warmed to 0 ºC and treated with AcOH (3 µL, 5×10^{-5} mmol) followed immediately by PhNCO (120 µL, 1.1 mmol). The reaction mixture was warmed to room temperature over 18 h then quenched with brine (4 mL). The organic material was extracted with CH_2Cl_2 (3 × 5 mL) and the combined extracts were dried (hydrophobic frit) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 13% EtOAc in hexane) gave thioamide **308**, (155 mg, 46%, 96% diastereoisomeric excess) as a colourless solid; m.p

116-117 ºC; $[\alpha]_D^{25}$= +56.8 (*c* 1.02, $CHCl_3$); ν_{max}/cm^{-1} (solid): 3184 (N-H), 2986 (C-H), 2926 (C-H), 2863 (C-H), 1670 (C=O), 1549 (C=S); ^{1}H NMR (600 MHz; $CDCl_3$, data for major diastereoisomer only): δ 1.56 (3H, s, C$\underline{H}_3$), 1.77 (3H, s, C$\underline{H}_3$), 2.39 (1H, dd, *J* 13.6, 9.8 Hz, 1 of C$\underline{H}_2$CC=S), 2.59 (1H, dd, *J* 13.6, 6.4 Hz, 1 of C$\underline{H}_2$CC=S), 2.95 (1H, tt, *J* 10.1, 5.9 Hz, C$\underline{H}$N), 3.26 (1H, dd, *J* 10.4, 8.5 Hz, 1 of OC$\underline{H}_2$), 3.86 (1H, dd, *J* 8.7, 5.6 Hz, 1 of OC$\underline{H}_2$), 4.01 (1H, d, *J* 9.8 Hz, C$\underline{H}$CH=CH_2), 5.08 (1H, dd, *J* 10.2, 1.1 Hz, CH=C$\underline{H}_2^{cis}$), 5.12 (1H, d, *J* 16.9 Hz, CH=C$\underline{H}_2^{trans}$), 6.69 (1H, dt, *J* 16.9, 9.8 Hz, C$\underline{H}$=CH_2), 7.11 (1H, t, *J* 7.3 Hz, aromatic C$\underline{H}$), 7.28-7.36 (5H, m, aromatic C$\underline{H}$), 7.40-7.45 (2H, m, aromatic C$\underline{H}$), 7.52-7.57 (2H, m, aromatic C$\underline{H}$), 11.31 (1H, s, N$\underline{H}$). ^{13}C NMR (150 MHz; $CDCl_3$, data for major diastereoisomer only): δ 22.0 ($\underline{C}H_3$), 24.0 ($\underline{C}H_3$), 33.5 ($\underline{C}H_2$CC=S), 59.9 ($\underline{C}$HCH=CH_2), 64.4 ($\underline{C}$HN), 68.6 (O$\underline{C}H_2$), 77.1 ($\underline{C}$C=S), 94.5 ($\underline{C}(CH_3)_2$), 118.1 (CH=$\underline{C}H_2$), 120.1 (aromatic $\underline{C}$H), 124.5 (aromatic $\underline{C}$H), 128.2 (aromatic $\underline{C}$H), 128.9 (aromatic $\underline{C}$H), 129.0 (aromatic $\underline{C}$H), 129.1 (aromatic $\underline{C}$H), 136.1 ($\underline{C}$H=CH_2), 137.7 (aromatic $\underline{C}$), 138.7 (aromatic $\underline{C}$), 168.7 ($\underline{C}$=O), 192.9 ($\underline{C}$=S); *m/z* (CI): 407 (MH^+, 8%), 349 (MH^+–$OC(CH_3)_2$, 23), 291 (100), 233 (73), 119 (28), 82 (69), 56 (28); HRMS (CI): $C_{24}H_{27}N_2O_2S$ (MH^+) requires: 407.1793; found 407.1796.

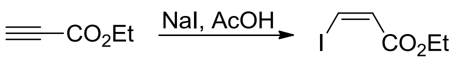
312. **(*S*,*Z*)-5-((3-Iodoallyl)thio)-3,3-dimethyl-*N*-phenyl-1,3,7,7a-tetrahydropyrrolo[1,2-*c*]oxazole-6-carboxamide**



212 **320** **312**

A stirred solution of thioamide **212** (241 mg, 1.41 mmol) in THF (10 mL) at 0 ºC was treated with *n*-butyllithium (2.5 M in hexanes, 0.619 mL, 1.42 mmol). The reaction mixture was stirred for 10 mins, cooled to –78 ºC then treated with allyl bromide **315** (383 mg, 1.55 mmol) in THF (4 mL). The reaction mixture was warmed to room temperature and stirred for 15 mins. The reaction mixture was quenched with brine (25 mL), saturated aq. $NaHCO_3$ solution (25 mL) and the organic material extracted with Et_2O (25 mL). The combined organic extracts were dried ($MgSO_4$) then concentrated *in vacuo* to give *N*,*S*-ketene acetal **320** as an orange oil which was dissolved in THF (1 mL). The solution was treated with PhNCO (0.15 mL, 1.4 mmol) then stirred for 1 h. The reaction mixture was treated with MeOH (1 mL) then concentrated *in vacuo* to give secondary amide **312** (457 mg, 71%) as an orange oil: ν_{max}/cm^{-1} (film): 3211 (br, N-H), 2983 (C-H), 2938 (C-H), 2874 (C-H), 1664 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.55 (3H, s, C<u>H</u>$_3$), 1.63 (3H, s, C<u>H</u>$_3$), 2.87 (1H, dd, *J* 16.6, 9.0 Hz, 1 of C<u>H</u>$_2$CC=O), 2.97 (2H, dd, *J* 16.6, 10.9 Hz, 1 of C<u>H</u>$_2$CC=O), 3.49 (1H, ddd, *J* 13.2, 6.8, 0.8 Hz, 1 of SC<u>H</u>$_2$), 3.68 (1H, t, *J* 8.7 Hz, 1 of OC<u>H</u>$_2$), 3.90 (1H, dd, *J* 13.2, 7.9 Hz, 1 of SC<u>H</u>$_2$), 4.24 (1H, dd, *J* 8.8, 7.0 Hz, 1 of OC<u>H</u>$_2$), 4.30-4.38 (1H, m, C<u>H</u>N), 6.33 (1H, q, *J* 7.5 Hz, C<u>H</u>=CHI), 6.50 (1H, d, *J* 7.5 Hz, CH=C<u>H</u>I), 7.05-7.11 (2H, m, aromatic C<u>H</u>), 7.29-7.34 (1H, m, aromatic C<u>H</u>), 7.57-7.60 (2H, m, aromatic C<u>H</u>), 9.59 (1H, br s, N<u>H</u>); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.9 (<u>C</u>H$_3$), 28.9 (<u>C</u>H$_3$), 34.9 (<u>C</u>H$_2$CC=O), 38.6 (S<u>C</u>H$_2$), 61.6 (<u>C</u>HN), 69.9 (O<u>C</u>H$_2$), 87.4 (CH=<u>C</u>HI), 96.1 (<u>C</u>(CH$_3$)$_2$), 119.6 (aromatic C<u>H</u>), 123.7 (aromatic C<u>H</u>), 123.9 (<u>C</u>=CS), 129.1 (aromatic C<u>H</u>), 135.5 (<u>C</u>H=CHI), 138.5 (aromatic <u>C</u>), 141.3 (C=<u>C</u>S), 162.7 (<u>C</u>=O); *m/z* (CI): 456 (MH^+, 8%), 416 (100), 289 (13), 170 (14); HRMS (CI): $C_{18}H_{21}N_2O_2SI$ (MH^+) requires: 456.0363; found 456.0366.

<u>313.</u> (*Z*)-Ethyl 3-iodoacrylate[142]



313

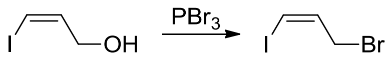
Prepared by the method of Paterson.[141] NaI (1.5 g, 10 mmol) was stirred under reduced pressure for 30 mins then treated with AcOH (10 mL) and ethyl propiolate (1.1 mL, 10 mmol). The mixture was heated to 70 ºC for 17 h then cooled to room temperature. The reaction mixture was diluted with Et_2O (10 mL), H_2O (10 mL) and the organic material extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with 2M NaOH solution (10 mL), brine (10 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 15% EtOAc in hexane) afforded acrylate **313**, (1.88 g, 83%) as a yellow oil: ν_{max}/cm^{-1} (film): 2981 (C-H), 2937 (C-H), 2904 (C-H), 1721 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (3H, t, *J* 7.2 Hz, CH$_2$C<u>H</u>$_3$), 4.25 (2H, q, *J* 7.2 Hz, C<u>H</u>$_2$CH$_3$), 6.89 (1H, d, *J* 9.0 Hz, ICH=C<u>H</u>), 7.44 (1H, d, *J* 9.0 Hz, IC<u>H</u>=CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3 (CH$_2$<u>C</u>H$_3$), 60.9 (<u>C</u>H$_2$CH$_3$), 94.9 (I<u>C</u>H=CH), 130.0 (ICH=<u>C</u>H), 164.7 (<u>C</u>=O).

<u>314.</u> (*Z*)-3-Iodoprop-2-en-1-ol[142]

313 **314**

A stirred solution of acrylate **313** (325 mg, 1.44 mmol) in CH_2Cl_2 (8 mL) at –78 ºC was treated with DIBAL-H (1 M in heptane, 4.3 mL, 4.3 mmol). The reaction mixture was stirred at –78 °C for 1 h then at 0 °C for 3 h. The reaction mixture was quenched with MeOH (8 mL) and stirred for 30 mins at 0 ºC then warmed to room temperature. The mixture was treated with 1M HCl solution (10 mL) and the organic material extracted with CH_2Cl_2 (2 × 8 mL). The combined organic extracts were washed with brine (8 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 30-50% Et_2O in hexane) gave alcohol **314**, (159 mg, 60%) as a colourless oil: ν_{max}/cm^{-1} (film): 3294 (br, O-H), 2920 (C-H), 2868 (C-H); ^1H NMR (600 MHz, $CDCl_3$) δ 4.25 (2H, d, *J* 6.0 Hz, $C\underline{H}_2OH$), 6.37 (1H, dd, *J* 7.5, 0.8 Hz, $IC\underline{H}{=}CH$), 6.50 (1H, dt, *J* 7.4, 5.7 Hz, $ICH{=}C\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 65.9 ($\underline{C}H_2OH$), 82.9 ($I\underline{C}H{=}CH$), 140.1 ($ICH{=}\underline{C}H$).

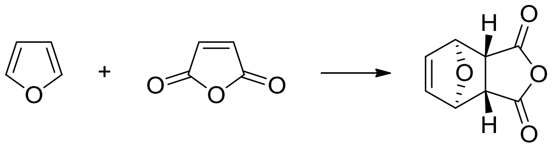
<u>315.</u> (*Z*)-3-Bromo-1-iodoprop-1-ene[152]



314 **315**

A stirred solution of alcohol **314** (805 mg, 4.38 mmol) in Et_2O (12.5 mL) at 0 ºC was treated with PBr_3 (0.16 mL, 1.8 mmol) then stirred for 1h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (15 mL) and the organic material extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with H_2O (15 mL), brine (15 mL), dried ($MgSO_4$) then concentrated *in vacuo* to give bromide **315** (865 mg, 80%) as an oil which was used in the next step without further purification: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2953 (C-H), 2924 (C-H), 2854 (C-H); ^1H NMR (600 MHz, $CDCl_3$) δ 4.01 (2H, d, *J* 7.2 Hz, $C\underline{H}_2Br$), 6.49 (1H, q, *J* 7.5 Hz, $ICH{=}C\underline{H}$), 6.53 (1H, d, *J* 7.5 Hz, $IC\underline{H}{=}CH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 32.7 ($\underline{C}H_2Br$), 88.2 ($I\underline{C}H{=}CH$), 136.6 ($ICH{=}\underline{C}H$).

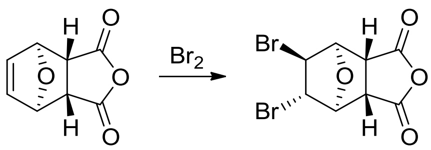
316. ***endo*-3a,4,7,7a-Tetrahydro-4,7-epoxyisobenzofuran-1,3-dione**



316

Prepared by the method of Curtis.[144] A stirred solution of maleic anhydride (17.5 g, 178 mmol) in Et_2O (50 mL) was treated with furan then stirred for 24 h. The mixture was cooled to 0 ºC and the precipitate was collected by filtration to give Diels-Alder adduct **316** (16.2 g, 55%) as a colourless solid: ν_{max}/cm^{-1} (solid): 3181 (br), 2974 (C-H), 2932 (C-H), 2876 (C-H), 1532; ^1H NMR (600 MHz; $CDCl_3$): δ 3.18 (2H, s, 2 × C<u>H</u>C=O), 5.46 (2H, s, 2 × C<u>H</u>O), 6.58 (2H, s, <u>H</u>C=C<u>H</u>); ^{13}C NMR (150 MHz; $CDCl_3$): δ 48.8 (2 × <u>C</u>HC=O), 82.3 (2 × <u>C</u>HO), 137.1 (<u>C</u>=<u>C</u>), 170.0 (2 × CH<u>C</u>=O).

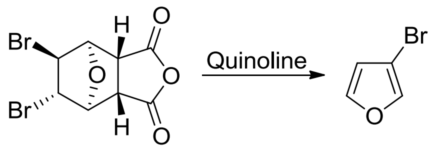
317. **(3a*R*,4*R*,5*S*,6*S*,7*S*,7a*S*)-5,6-dibromohexahydro-4,7-epoxyisobenzofuran-1,3-dione**



316 **317**

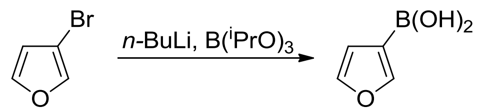
Prepared by the method of Curtis.[144] A stirred solution of Diels-Alder adduct **316** (9.02 g, 54.3 mmol) in CH_2Cl_2 (250 mL) was treated with Br_2 (2.79 mL, 54.3 mmol) then stirred for 4 h. A precipitate formed which was collected by filtration. The filtrate was concentrated *in vacuo* to give a solid which was washed with Et_2O (100 mL). The precipitate was combined with the solid and washed with Et_2O (100 mL) to give dibromide **317** (11.1 g, 63%) as a colourless solid: ν_{max}/cm^{-1} (solid): 3037 (C-H), 3014 (C-H), 2993 (C-H), 1777 (C=O); ^1H NMR (600 MHz, acetone-d_6) δ 3.95 (1H, d, *J* 7.2 Hz, C<u>H</u>C=O), 4.17 (1H, d, *J* 7.5 Hz, C<u>H</u>C=O), 4.47 (1H, d, *J* 3.4 Hz, C<u>H</u>Br), 4.60 (1H, dd, *J* 4.9, 3.4 Hz, C<u>H</u>Br), 5.07 (1H, s, C<u>H</u>CHC=O), 5.27 (1H, d, *J* 4.9 Hz, C<u>H</u>CHC=O); ^{13}C NMR (150 MHz, acetone-d_6) δ 47.7 (<u>C</u>HC=O), 50.1 (<u>C</u>HC=O), 53.1 (<u>C</u>HBr), 53.2 (<u>C</u>HBr), 84.8 (<u>C</u>HCHC=O), 88.5 (<u>C</u>HCHC=O), 170.8 (<u>C</u>=O), 172.3 (<u>C</u>=O).

318. 3-Bromofuran



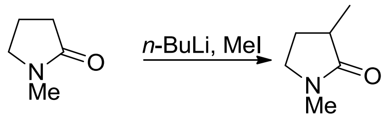
A stirred suspension of dibromide **317** (7.76 g, 23.8 mmol) in quinoline (5.62 mL, 47.6 mmol) was heated to 215 ºC for 1 h. The mixture was distilled (215 ºC, 760 mmHg) to give bromide **318** (970 mg, 28%) as a colourless oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2959 (C-H), 2917 (C-H), 2849 (C-H); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.45 (1H, d, *J* 1.1 Hz, C<u>H</u>CBr), 7.37 (1H, t, *J* 1.7 Hz, CH=C<u>H</u>O), 7.44 (1H, s, C=C<u>H</u>O); ^{13}C NMR (150 MHz, $CDCl_3$) δ 99.7 (<u>C</u>=CHO), 113.5 (<u>C</u>H=CHO), 141.1 (C=<u>C</u>HO), 143.7 (CH=<u>C</u>HO).

319. Furan-3-ylboronic acid



Prepared by the method of Beaulieu.[145] A stirred solution of bromide **318** (164 mg, 1.12 mmol) and B(^{i}PrO)$_3$ (0.284 mL, 1.23 mmol) in THF (2 mL) was cooled to –78 ºC. The solution was treated dropwise with *n*-butyllithium (2.5 M in hexanes, 0.470 mL, 1.18 mmol) then stirred for 40 mins. The reaction mixture was warmed to 0 ºC, quenched with 3M HCl solution (3 mL) and the organic material extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) then concentrated *in vacuo* to give a solid which was triturated at 50 ºC in a 3:1 mixture of hexane-Et_2O. The suspension was filtered to give boronic acid **319** (57 mg, 45%) as a grey solid: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2918 (C-H), 2849 (C-H); ^{1}H NMR (600 MHz; DMSO-d_6): δ 6.63 (1H, d, *J* 1.2Hz, CC<u>H</u>=CHO), 7.63 (1H, t, *J* 1.5Hz, CCH=C<u>H</u>O), 7.83 (1H, s, BC=C<u>H</u>O), 7.93 (2H, s, B(O<u>H</u>)$_2$); ^{13}C NMR (150 MHz; DMSO-d_6): δ 113.7 (C<u>C</u>H=CHO), 116.0 (br, B<u>C</u>=CH), 142.7 (CCH=<u>C</u>HO), 150.2 (BC=<u>C</u>HO).

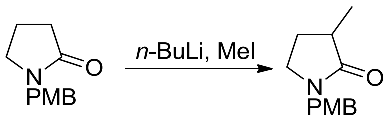
<u>324.</u> 1,3-Dimethylpyrrolidin-2-one[153]



324

A stirred solution of *N*-methylpyrrolidin-2-one (4.86 mL, 50.4 mmol) in THF (60 mL) at –78 ºC was treated dropwise with *n*-butyllithium (2.5 M in hexanes, 22.2 mL, 55.4 mmol) and stirred for 30 minutes. The reaction mixture was treated dropwise with MeI (3.77 mL, 60.5 mmol) then warmed to room temperature over 2.5 h. The reaction mixture was quenched with saturated aq. NH_4Cl solution (40 mL) and the organic material extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with H_2O (40 mL), brine (40 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2; 50-100% EtOAc in petroleum ether) gave lactam **324** (1.30 g, 23%) as a yellow oil: ν_{max}/cm^{-1} (CH_2Cl_2 cast): 2964 (C-H), 2932 (C-H), 2874 (C-H), 1671 (C=O); ^{1}H NMR (500 MHz; $CDCl_3$): δ 1.18 (3H, d, *J* 7.3 Hz, $CHC\underline{H}_3$), 1.61 (1H, dq, *J* 12.6, 8.4 Hz, 1 of $C\underline{H}_2CH_2N$), 2.19-2.26 (1H, m, 1 of $C\underline{H}_2CH_2N$), 2.43 (1H, sxt, *J* 7.6 Hz, $C\underline{H}C{=}O$), 2.83 (3H, s, $NC\underline{H}_3$), 3.27 (2H, dd, *J* 8.5, 5.4 Hz, $C\underline{H}_2NCH_3$); ^{13}C NMR (125 MHz; $CDCl_3$): δ 16.5 ($CH\underline{C}H_3$), 27.1 ($\underline{C}H_2CH_2N$), 29.8 ($\underline{C}HC{=}O$), 36.5 ($N\underline{C}H_3$), 47.5 ($\underline{C}H_2NCH_3$), 177.4 ($\underline{C}{=}O$); *m/z* (EI): 113 (M^+, 30%), 44 (100); HRMS (EI): $C_6H_{11}NO$ (M^+) requires: 113.0835; found 113.0840.

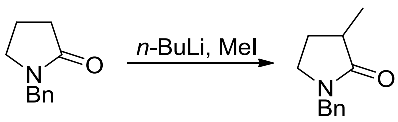
<u>325.</u> 1-(4-Methoxybenzyl)-3-methylpyrrolidin-2-one



192 **325**

A stirred solution of lactam **192** (0.50 g, 2.4 mmol) in THF (25 mL) at –78 ºC was treated dropwise with *n*-butyllithium (2.5 M in hexanes, 1.1 mL, 2.7 mmol) and stirred for 30 mins. The reaction mixture was treated dropwise with MeI (0.182 mL, 2.93 mmol) then warmed to room temperature over 1.5 h. The reaction was quenched with saturated aq. NH_4Cl solution (25 mL) and the organic material extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50-60% EtOAc in hexane) gave lactam **325** (402 mg, 75%) as a yellow oil: ν_{max}/cm^{-1} ($CDCl_3$ cast): 2961 (C-H), 2931 (C-H), 2872 (C-H), 1680 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (3H, d, *J* 7.2 Hz, $CHC\underline{H}_3$), 1.58 (1H, dq, *J* 12.4, 8.3 Hz, 1 of $C\underline{H}_2CH_2N$), 2.14-2.23 (1H, m, 1 of $C\underline{H}_2CH_2N$), 2.50 (1H, sxt, *J* 7.5 Hz, $C\underline{H}CH_3$), 3.11-3.18 (2H, m, $C\underline{H}_2NCH_2Ar$), 3.79 (3H, s, $C\underline{H}_3O$), 4.36 (1H, d, *J* 14.3 Hz, 1 of $NC\underline{H}_2Ar$), 4.40 (1H, d, *J* 14.3 Hz, 1 of $NC\underline{H}_2Ar$), 6.85 (2H, d, *J* 8.3 Hz, $CH_2CC\underline{H}$=CH), 7.15 (2H, d, *J* 8.7 Hz, CH_2CCH=C$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.5 ($CH\underline{C}H_3$), 27.1 ($\underline{C}H_2CH_2N$), 37.0 ($\underline{C}HCH_3$), 44.6 ($\underline{C}H_2NCH_2Ar$), 46.3 ($CH_2N\underline{C}H_2Ar$), 55.4 ($\underline{C}H_3O$), 114.1 ($CH_2C\underline{C}H$=CH), 128.9 ($CH_2\underline{C}CH$=CH), 129.6 (CH_2CCH=$\underline{C}$H), 159.1 ($CH_3O\underline{C}$), 177.4 ($\underline{C}$=O); *m/z* (EI): 219 (M^+, 100%); HRMS (EI): $C_{13}H_{17}NO_2$ (M^+) requires: 219.1254; found 219.1263.

<u>326.</u> 1-Benzyl-3-methylpyrrolidin-2-one[154]



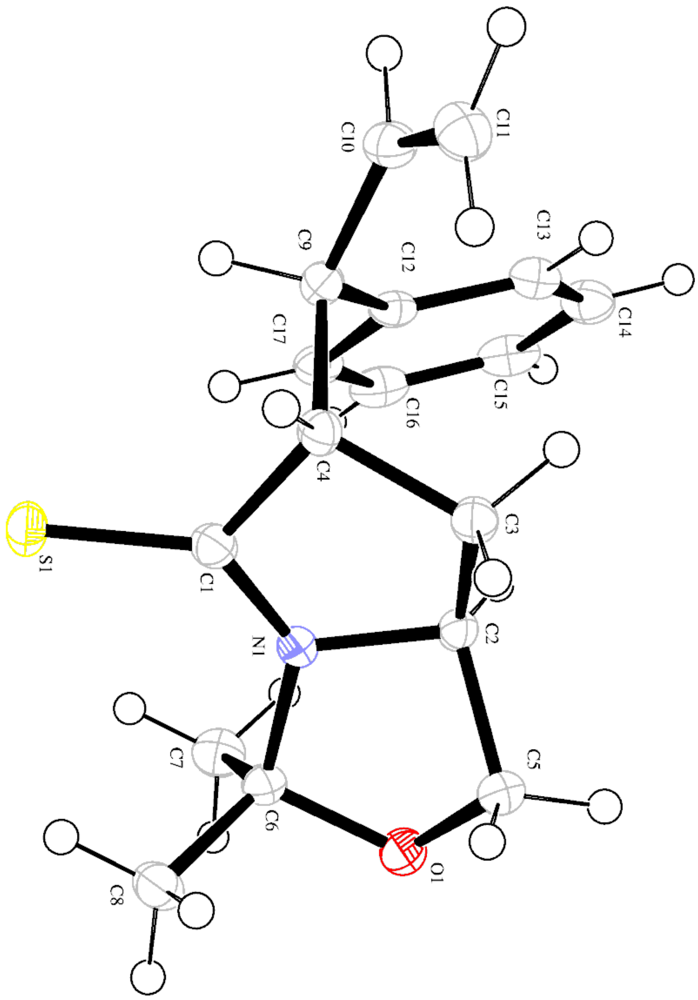
326

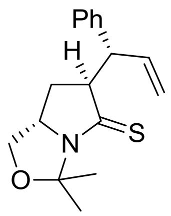
A stirred solution of *N*-benzylpyrrolidin-2-one (1.80 mL, 11.4 mmol) in THF (33 mL) at –78 ºC was treated dropwise with *n*-butyllithium (2.5 M in hexanes, 5.50 mL, 13.7 mmol) and stirred for 30 mins. The reaction mixture was treated dropwise with MeI (1.40 mL, 22.8 mmol) and stirred for 30 mins. The reaction mixture was warmed to room temperature and stirred for 1.5 h and then quenched with saturated aq. NH_4Cl solution (30 mL). The organic material was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were washed with H_2O (30 mL), brine (30 mL), dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 50% EtOAc in petroleum ether) gave lactam **326** (1.55 g, 72%) as a yellow oil: ν_{max}/cm^{-1} (film): 2965 (C-H), 2930 (C-H), 2872 (C-H), 1677 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.24 (3H, d, *J* 7.2 Hz, $CHC\underline{H}_3$), 1.59 (1H, dq, *J* 12.7, 8.4 Hz, 1 of $C\underline{H}_2CH_2N$), 2.21 (1H, dddd, *J* 12.6, 8.6, 6.7, 4.1 Hz, 1 of $C\underline{H}_2CH_2N$), 2.47-2.56 (1H, m, $C\underline{H}CH_3$), 3.15-3.19 (2H, m, $C\underline{H}_2NCH_2Ph$), 4.43 (1H, d, *J* 14.7 Hz, 1 of $NC\underline{H}_2Ph$), 4.47 (1H, d, *J* 14.7 Hz, 1 of $NC\underline{H}_2Ph$), 7.20-7.36 (5H, m, aromatic C$\underline{H}$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.6 ($CH\underline{C}H_3$), 27.2 ($\underline{C}H_2CH_2N$), 36.9 ($\underline{C}HCH_3$), 44.8 ($\underline{C}H_2NCH_2Ph$), 46.9 ($CH_2N\underline{C}H_2Ph$), 127.6 (aromatic $\underline{C}$H), 128.2 (aromatic $\underline{C}$H), 128.8 (aromatic $\underline{C}$H), 136.8 (aromatic $\underline{C}$), 177.5 (C=O); *m/z* (EI): 189 (M^+, 63%), 92 ; HRMS (EI): $C_{12}H_{15}NO$ (M^+) requires: 189.1148; found 189.1152.

5. APPENDICES

5.1 X-ray crystallography data

(6*S*,7a*S*)-3,3-dimethyl-6-((*R*)-1-phenylallyl)tetrahydropyrrolo[1,2-*c*]oxazole-5(3*H*)-thione





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Empirical formula	$C_{17}H_{21}NOS$	
Formula weight	287.41	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.737(3) Å	α = 90°
	b = 13.515(4) Å	β = 90°
	c = 14.881(5) Å	γ = 90°
Volume	1556.0(9) Å^3	
Z	4	

Density (calculated)	1.227 Mg / m^3
Absorption coefficient	0.204 mm^{-1}
F(000)	616
Crystal	Plate; Colourless
Crystal size	0.42 × 0.30 × 0.06 mm^3
θ range for data collection	2.97 – 30.51°
Index ranges	$-11 \leq h \leq 10$, $-19 \leq k \leq 19$, $-21 \leq l \leq 21$
Reflections collected	18869
Independent reflections	4743 [R_{int} = 0.0433]
Completeness to θ = 30.51°	99.9 %
Absorption correction	Semi−empirical from equivalents
Max. and min. transmission	0.9879 and 0.9193
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4743 / 0 / 183
Goodness-of-fit on F^2	1.047
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0366, $wR2$ = 0.0799
R indices (all data)	$R1$ = 0.0392, $wR2$ = 0.0813
Absolute structure parameter	0.07(5)
Largest diff. peak and hole	0.234 and −0.219 e Å^{-3}

5.2 References

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